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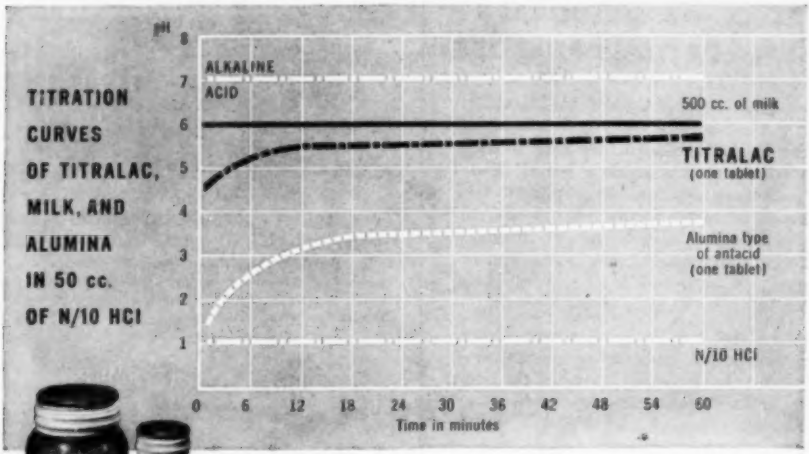

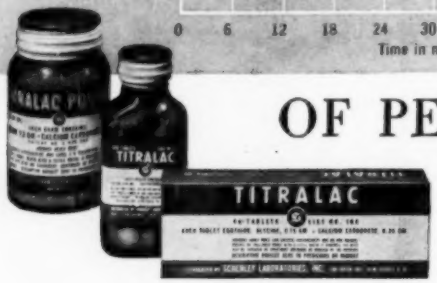

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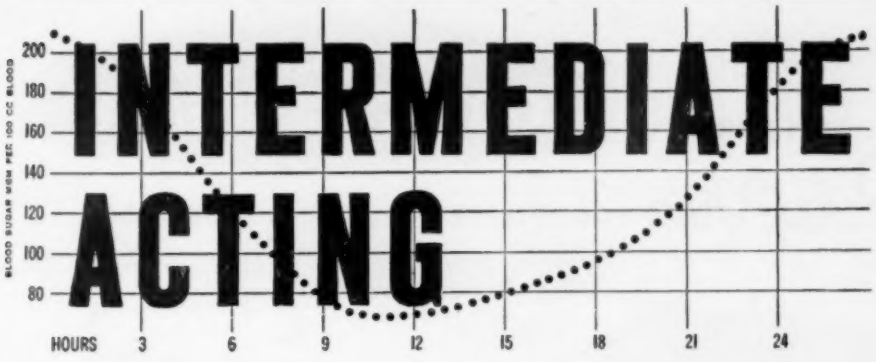

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ANNALS OF
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VOLUME 32 JANUARY, 1950 NUMBER 1

THE USE OF ISOTOPES AS METABOLIC TRACERS *

By DEWITT STETTEN, JR., *New York, N. Y.*

WHEN the chemist approaches the study of a biological system, his first enquiry is usually at the analytical level, namely, the identification and quantitative determination of the reactants. Having answered these purely analytical questions, he must next undertake the pursuit of more elusive matters. What reactions do these reactants undergo in the body? How are they formed, and how destroyed? What are the normal rates of these several reactions, and how do these rates vary in response to such variables as growth, disease, drug action and altered nutrition?

It is unfortunate that the answers to such questions cannot, in general, be found by the observation of a completely normal intact animal. To permit the study of an isolated reaction, the experimenter is often forced to resort to more or less drastic procedures. He may be compelled to eliminate the liver from the animal, or what is even worse, he may remove the animal from its liver. Having thus isolated the liver, he may have to proceed even further, slicing it or mincing it prior to studying the reactions in which he is interested. Strange as it may seem, vast amounts of important information have been gleaned from the study of such abused tissues but it is apparent that a certain caution must be observed in the translation of results obtained by these means back to the normal intact animal. It is likewise apparent that a subtler approach, one involving less trauma to the animal and freeing the investigator from the difficult decision of the extent to which the experimental procedure has distorted reactions and reaction rates from normal values, would be very desirable. What has become known as the tracer technic is an approximate answer to this need.

It may be pointed out that the tracer technic, which involves the labeling of a molecule in such a fashion that it or its derivatives are recognizable to the experimenter, is much more ancient than is the biological use of isotopes. Probably the most important example of early tracer studies was Knoop's

* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 31, 1949.

investigation [1] of the mode of degradation of fatty acids in the body of the intact animal by the expedient of replacing a hydrogen atom of the fatty acid molecule by a benzene nucleus. Pursuit of this aromatically labeled molecule gave us our first clear insight into the mechanism known to all of you as Beta-oxidation. Such labeling was useful but it still was far from ideal. The aromatic acids of Knoop differed widely in their chemical and physical properties from the naturally occurring aliphatic fatty acids and there was reason to suspect that the experimental animal could discriminate between the two types of compounds and did not necessarily treat them in identical fashion. Clearly what was required was a labeled molecule which on the one hand, so simulated its naturally occurring analog as to deceive the experimental animal and on the other hand, could readily be detected and quantitatively estimated by the experimenter. These requirements appear to be almost ideally met if one employs the isotopes of the elements of organic chemistry, carbon, hydrogen, nitrogen, oxygen, sulfur, phosphorus, iodine, and so forth, replacing an atom in any molecule by its stable or radioactive isotope. The resultant product is extraordinarily similar in properties to the parent compound yet, with suitable measuring instruments, the physicist can readily determine the quantity of isotope present in it or its derivatives. The increasing availability of isotopes, the development of methods for the introduction of isotopic atoms into various compounds, and the improvement of methods for the measurement of isotopic abundance, over the past 15 years, have placed a new and powerful tool at the disposal of the physiological chemist, permitting him to confirm the occurrence in the intact animal of reactions which had formerly been demonstrated only in such materials as liver slices, and allowing him to measure reaction rates in the intact animal with an elegance previously unknown.

In the simplest type of experiment, in which the question is whether a particular dietary or body constituent is converted in the body into some other product, one has merely to synthesize the suspected precursor in such a fashion as to include one or more isotopic atoms, administer it to the animal, and, after a period of time, isolate the suspected product from the tissues or excreta. The presence of isotope in the product is prima facie evidence that the suspected transformation has taken place. Numerous examples of reactions which have been proved, with the aid of isotopes, to occur might be cited; among these the conversion of palmitic into stearic acid,[2] and vice versa,[3] the conversion of serine into cystine, ethanolamine,[4] and glycine,[5] the conversion of proline into ornithine, glutamic acid and hydroxyproline,[6] the conversion of cholesterol into cholic acid,[7] and pregnandiol,[8] will serve as examples.

More interesting, perhaps, are those studies in which the primary question has been the rate of synthesis or the rate of destruction of some body constituent. The particular case of the rate at which some body constituent is being simultaneously synthesized and degraded while the quantity of constituent remains sensibly constant has attracted attention and has given

rise to the concept of "turnover." Thus, it was early shown that in the animal at constant weight and uniform nutrition, even though the quantity of depot fat remained constant, each day a portion of this depot fat was mobilized and degraded while an equivalent amount of newly synthesized depot fat made its appearance. In studies of this sort, the rate of turnover could be computed from the rate of change in the isotope concentration of the body constituent, either following the administration of the isotopically labeled constituent proper, or during a period of administration of an isotopically labeled precursor of the material in question.

By the application of such technics it has been shown that the half-life of the depot fatty acids is five to six days in the mouse,[9] and about nine days in the rat.[10] In other words, even though the total quantity of fatty acids in the depot fat of the rat is the same at the beginning and at the end of the experiment, after about nine days half of the molecules initially present will have been replaced by newly synthesized molecules. Thus, the depot fat is not the relatively inert reservoir that might have been supposed, but is in a steady state only insofar as the rate of its mobilization, which is rapid, is matched by the rate of its deposition.

The rates of turnover of several other body constituents have similarly been calculated from observations of the rate of change of isotope concentration in these substances under suitable conditions, while the animal was kept at constant body weight and on a uniform diet. The relatively sluggish turnover of liver glycogen,[11] under these circumstances, contrasts with the rapid rate at which glycogen reappears in the liver when, following its elimination by fasting, a glycogen precursor is fed. This contrast points out very clearly one of the advantages of the isotope technic in that it permits the estimation of the rate of glycogenesis without the necessity of subjecting the animal to previous fast, an experimental procedure which seriously affects the very rate under study.

Whereas the adult animal has been found to turn over each day considerably more fat than glycogen, the application of the same methods to the fetus revealed that the situation here was quite different.[12] Per gram of wet weight the fetus makes and destroys each day much more glycogen than does its parent. In this regard, another convenient application of the isotope technic may be mentioned, namely, the study of passage across a body membrane of some particular substance. In the course of the studies on fetal tissues just mentioned, isotopic fatty acids and isotopic cholesterol were fed to the maternal organism, and the presence of isotope demonstrated in the corresponding constituents of the fetus, proving clearly that these molecules did pass across the placenta.

If one impresses certain variables upon experiments of the type just cited, one finds that the normal rates are subject to striking variation. Thus, in the animal rendered diabetic, we find that one of the defects is a marked inhibition of the rate of synthesis of fatty acids, this rate falling to a matter of 5 per cent of normal.[13] Conversely, if insulin is administered to the other-

wise normal rabbit, one observes a marked enhancement of this rate, fatty acids being synthesized in the liver some four times as rapidly as normal.[14] These effects of the level of insulin supply upon the rate of fatty acid synthesis fit in nicely with current theories of insulin function,[15] and must be taken into account when considering the loss in fat in uncontrolled diabetes and the gain in depot fat observed when insulin is administered to either the normal or the diabetic individual.

The examples which I have mentioned are intended to give an idea of the types of problem in which isotopes as tracers have proved of great importance. I have excluded from this presentation the use to which radioactive isotopes may be put as sources of radiant energy, which is yet another field of application. Used as tracers, there would appear to be certain types of problems to which isotopes lend themselves particularly well, and among these are:

1. The study of the anatomical distribution of a substance. Here the special technic of radio-autography offers much promise.
2. The study of the biological precursors and derivatives of a substance. The isotopic evidence adduced in questions of this sort is usually very clear and unambiguous.
3. The study of the rate of turnover of a body constituent in the organism while in a "steady state." In most cases the only technic at present available for the solution of problems of this type is that under discussion.
4. As a corollary to the foregoing, the study of changes in normal reaction rates under various abnormal circumstances.

It is clear that the use of isotopic tracers is a valuable adjuvant in research in intermediary metabolism. I should like to stress again what has been stressed before, that it in no way supplants the other technics of biochemical investigation but rather permits of a more powerful and direct application to biological problems of the technics upon which the chemist must always ultimately depend, namely, synthesis and analysis.

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CRYOGLOBULINEMIA. I. REPORT OF TWO CASES WITH DISCUSSION OF CLINICAL MANIFESTATIONS, INCIDENCE AND SIGNIFICANCE*

By David P. Barr, M.D., F.A.C.P., George G. Reader, M.D., and Charles H. Wheeler, M.D., *New York, N. Y.*

The term, cryoglobulinemia, was proposed by Lerner and Watson [28] in 1947 in describing a patient whose serum contained a cold precipitable protein and whose presenting symptom was an extensive purpura that developed when he was exposed to the cold. They suggested that the designation of cryoglobulin be applied to any one of a group of proteins with the common property of precipitating or gelifying from cooled serum and that it include those proteins which in high concentration may precipitate at room temperature. Interest in the case of purpura led Lerner, Barnum and Watson [26] to a search for similar proteins in a variety of clinical conditions and to successful recovery of cold precipitable proteins in amounts greater than 10 mg. per cent in one or more cases of lymphatic leukemia, bronchiectasis, rheumatic fever and subacute bacterial endocarditis. Smaller amounts not estimated quantitatively were found in several other diseases.

Review of the literature by Lerner and Watson disclosed the record of two other cases of purpura induced by exposure to cold and several widely scattered reports of cold precipitable proteins encountered in large amounts most often in association with multiple myeloma and kala azar, but also in isolated instances of arthritis and hepatic disease. Manifestations in these cases were more numerous and included not only cold sensitivity and purpura, but also Raynaud's phenomena, mottling of the extremities, bleeding from the nose and gums, extensive retinal hemorrhages, progressive deafness, agglomeration or agglutination of red blood cells with rouleaux formation and a rapid sedimentation rate.

Our attention was called to the subject by the recognition of cryoglobulinemia in two patients who entered the New York Hospital during the winter of 1948.

Case 1. The first patient was seen in consultation with Dr. Willis A. Murphy. He was an insurance executive, aged 54, who for 10 years had suffered from a polymorphic purpuric eruption induced by exposure to cold and disappearing in summer or during periods in winter when he went to Florida. Attacks were characterized by the appearance of hundreds of macular purpuric spots ranging in size from 1 to 20 mm. in diameter. There were also edematous, raised, tender lesions with purpuric base, patches of urticaria, irregular papillomatous lesions and localized hyperkeratoses, which were exquisitely tender to the lightest pressure. One raised wheal with pur-

* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 29, 1949.

From the Department of Medicine of the New York Hospital-Cornell University Medical Center.

puric base, on the left hand, had been recurrent over many months, tending to swell after meals and subsiding during the night. On one occasion the eruption consisted of vesicles which were at first clear and later became hemorrhagic. During the attacks he suffered almost intolerable itching and while standing experienced intense

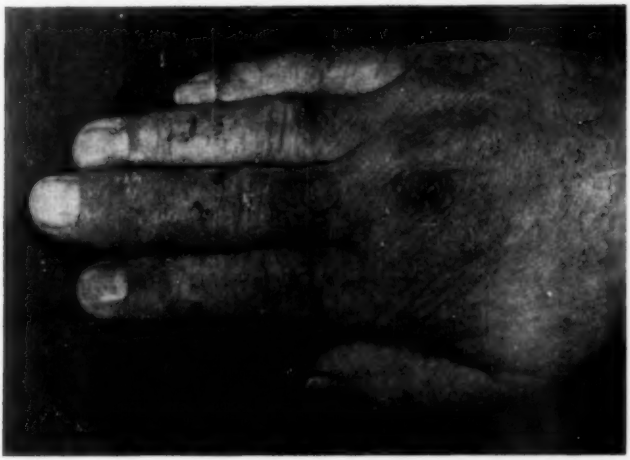

FIG. 1. *A*. Photograph of right hand of case 1 showing swollen, tender purpuric lesions.

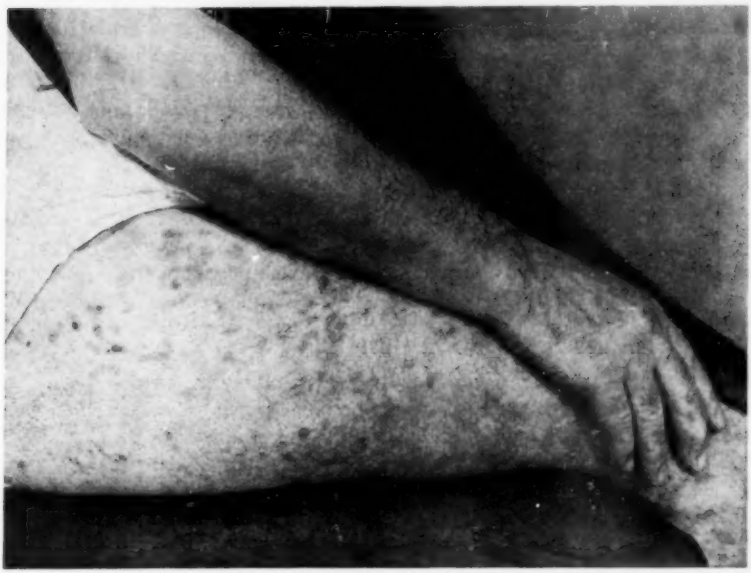

FIG. 1. *B*. Photograph of right arm and thigh of case 1 showing distribution of purpura.

burning pain in the feet. The character of some of the lesions is portrayed in figure 1.

Accompaniments of the eruption included at one time or another purplish red swelling of the joints without fever or leukocytosis, abdominal distress sometimes followed by diarrhea, hemorrhages from the gums and nose, blisters in the oral mucous membrane and muscular cramps. One particularly severe attack of cutaneous and oral involvement was preceded by intense vertigo.

Examination revealed the purpuric eruption in a florid phase, a bilateral nerve conduction deafness, enlarged and scarred tonsils, a liver enlarged 8 cm. below the costal margin in the mid-clavicular line, and stiffness and tenderness of knees and ankles and the left metatarsophalangeal joints. The spleen was not palpated and lymph nodes were not enlarged. There was no anemia. Red blood cells 4.6 million; hemoglobin 15.2 grams; white blood cells 8,000 with a normal distribution of cells in the smear; platelets 300,000; bleeding time 2 minutes; clotting time 21 minutes, clot retraction rapid; prothrombin 84 per cent; serum calcium 10.8 mg. per cent. Tourniquet and flick tests were negative.

By the usual laboratory methods the concentration of total protein in the serum was found to be 7.4 grams per cent, 3.5 grams per cent of which was globulin. The clear cut relationship of cold to the development of attacks and the high value of serum globulin suggested the possible presence of a cryoglobulin which by appropriate methods was found to exist in heavy trace and to have a value of 22 mg. per cent in the serum.

Before this interesting disclosure could be adequately investigated, the patient partially recovered and left for Florida. Efforts to obtain further data concerning him have as yet been unsuccessful.

Comment. The number of thrombocytes and the bleeding time in this patient were normal. Other laboratory tests indicated no hemorrhagic tendency or fault in the clotting mechanism. At first the polymorphic eruption was thought to resemble Henoch's purpura, a diagnosis which was suggested also by the abdominal symptoms and the joint manifestations. In some respects the condition was not unlike Sack's [45] case of vascular purpura which was induced by exposure to cold, and the case reported by Horton and Peters [22] in which purpura was produced by swimming in cold water and corrected by wrapping in blankets and which was regarded as an instance of cold allergy. It also resembled the *purpura hyperglobulinemica* described by Waldenström [54] and others.[7, 24, 30]

It is unfortunate that circumstances prevented adequate study. Nothing can be said concerning the cause of the elevated globulin or the presence of the cold precipitable protein. No statement can be made about the possibility of an underlying multiple myeloma or myelosis, since sternal aspiration was not performed and extensive skeletal roentgen-rays were lacking.

The cryoglobulin appeared as a flocculent precipitate when the serum was cooled and was readily dissolved when the tube was warmed to 37° C. The amount was small, only 22 mg. per cent, as compared with the 800 mg. per cent of Lerner and Watson's case and the very much higher values in other cases in the literature. The reasons for considering it significant were the symptoms which simulated those described by Lerner and Watson and the history of induction of attacks by exposure to cold.

Case 2. The second patient presented a much more varied symptomatology and was intensively studied over a period from December 10, 1947 until the time of his death over 12 months later. He was a Russian Jewish manufacturer, 58 years of age, who for five years had suffered symptoms suggestive of chronic gout. When first seen on April 16, 1945 he exhibited a hot red swelling of the right great toe and a value of blood uric acid of 4.8 mg. per cent. Treatment with colchicine promptly relieved his symptoms. At that time he had no anemia. No difficulty was encountered in obtaining blood specimens and his sedimentation rate by the Westergren method was 8 mm. in 45 minutes.

He was not seen again until December 10, 1947 when he complained that for a year he had been easily fatigued and that during the winter, exposure to cold had regularly caused numbness, pain and conspicuous pallor of his toes and fingertips and a mottled blanching of the skin of the ears and face. For three months his gums had bled and he had had frequent nocturnal epistaxes. Rectal bleeding which had been troublesome for about a year had been attributed to hemorrhoids. For two weeks he had noted slight dimness of vision.

Examination revealed cyanosis with innumerable minute dilated blood vessels in the skin of the face, pallor of the oral mucosa, and boggy pallor of the nasal mucosa with dilated blood vessels and small bleeding points in Kiesselbach's area on both sides. Funduscopic examination showed irregularly narrowed retinal arterioles with small superficial retinal hemorrhages. The color and temperature of the hands and feet did not appear remarkable at rest. Upon elevation both feet and legs blanched unduly and when dependent became cold and presented a curious mottling. This consisted of a gradually deepening cyanosis in which numerous discrete, irregularly shaped, pallid areas developed as the veins distended and pressed upon the under surface of the skin. Both cyanosis and mottling disappeared when the legs were restored to the horizontal position. Applications of ice to the hands and feet did not induce abnormal blanching. Pulsations in the radial, ulnar, dorsalis pedis and posterior tibial arteries were easily palpable. Oscillometric readings were normal in the hands, wrists, feet and ankles. Blood pressure was 160 mm. of mercury systolic and 105 diastolic. The liver was palpable two fingers'-breadth below the costal margin. There were several small internal and external hemorrhoids. Proctoscopic examination revealed no bleeding points or other abnormalities.

Laboratory investigation at the time he was first admitted to the New York Hospital revealed anemia with hemoglobin of 12.0 gm. and 3.7 million red blood cells, a blood uric acid of 7.9 mg. per cent with urea nitrogen of 15 mg. per cent. Phenolsulfonephthalein excretion was 75 per cent; urea clearance was 80.6 and 66.6 per cent. Thymol turbidity was 12 units and bromsulfalein retention 4.6 per cent. Other tests for liver function, including cephalin flocculation, serum bilirubin and prothrombin time, were within normal limits. Bleeding time was one minute, clotting time four minutes by the capillary tube method, and platelet count was 330,000. Clot retraction required 13 hours for completion. Values for total serum protein, albumin and globulin on two occasions were determined as: total protein 7.7–6.3; albumin 4.9–3.7; globulin 2.6–2.6. Roentgen-rays of the right great toe were interpreted as suggesting osteoarthritis rather than gout. Initially no satisfactory formulation of the condition was made.

Constant difficulty was encountered in withdrawal of venous blood. It was found necessary to use a large needle and to warm the syringe in order to obtain adequate amounts. Finger blood collected for red blood cell counts tended to clot prematurely. Rouleaux formation was prominent in smears and blood collected in pipettes formed red sand which made counting of cells difficult. Examination of hanging drop preparations showed abundant precipitate which surrounded and enmeshed the blood cells. Furthermore with potassium oxalate and heparin as well as with defibrination

of the blood, marked sedimentation of the red cells with jelling which resembled clot formation occurred in the collecting bottles. With potassium oxalate at room temperature jelling was so prompt that no estimation of sedimentation rate was possible. Even at 37° C. the results could not be accurately interpreted. With sodium citrate settling of red blood cells, both at room temperature and at 37° C., was very rapid but was sufficiently gradual to permit precise observation. These phenomena were so striking that they led to special studies of the suspension stability and sedimentation rate by Dr. Hugh Luckey who will report them in a separate communication.[31]

They also suggested the diagnosis of multiple myeloma which was confirmed by sternal bone marrow aspiration. This revealed 88,000 cells per cu. mm. and 42 per cent myeloma cells per 100 normal marrow cells in the smear. A roentgenogram of the skull showed multiple small radiolucent areas and some osteoporosis with longitudinal striation in the bodies of the vertebrae. Repeated examination of the urine failed to disclose the presence of Bence Jones protein.

At this time it was recalled that many of the symptoms presented by the patient were similar to those of a case of multiple myeloma reported in 1933 by Wintrobe and and Buell [57] and exhibiting in the serum a protein which was precipitable at room temperature. Because of this the proteins of the serum were reëstimated with the single variation in technic that the blood was kept at 37.5° C. until the clot had completely retracted and the specimen had been centrifugated at 37.5° C. This procedure revealed a value of 15.2 grams per cent for total protein, 4.2 for albumin and 11.0 for globulin, 8.9 grams per cent of which was cold precipitable.

TABLE I

Serum Electrophoretic Fractionation

Peak	Sample 1 3/12/48 Gm. %	Sample 2 4/2/48 Gm. %	Approx. Normal Average Gm. %
Alb.	3.84	2.72	3.79
α 1	0.54	0.40	0.41
α 2	1.30	0.78	0.61
α 3 or M_1	0.36	0.26	—
β	0.48	0.44	0.86
γ 1	0.12	0.12	0.20
γ 2	0.24	0.42	0.74
M	0.33	1.14	—
Total	7.21	6.28	6.84

Electrophoretic analysis of the proteins of the serum was made by Dr. Mary Petermann of the Sloan-Kettering Institute. Since even at room temperature the cryoglobulin precipitated in the veronal buffer of Longsworth at Ph 8.6, ionic strength 0.1, it could not be examined electrophoretically by the usual procedure. The supernatant serum obtained after removal of the cryoglobulin was analyzed on two occasions with results indicated in table 1 where, for convenience of comparison, the approximate normal values as determined by Petermann and Hogness [38] have been included.

The analysis indicated a moderate elevation of total globulin with two abnormal peaks. It showed also an increase in alpha globulins and lower than normal beta and gamma fractions separate. Detailed analysis of the cryoglobulin which was later purified revealed it as a homogeneous protein resembling a gamma globulin with an electrophoretic mobility of 3.4×10^{-5} in acetate buffer Ph 4.7 ionic strength 0.1.

Epistaxes, most troublesome at night, and almost constant and often excessive

oozing of blood from the gums, resulted in progressive anemia which could be controlled only by repeated transfusions. Examination of the eyegrounds revealed increasing edema about the optic discs. The fundi became spattered with hemorrhages of all sizes and shapes, a number of them containing white centers. There was some venous stasis and arterial venous compression became increasingly evident. The electrocardiogram, originally regarded as normal, revealed later variable changes possibly indicative of disturbed coronary circulation. Tinnitus became a prominent symptom and was accompanied by progressive bilateral nerve deafness. Complaints of occipital headache, vertigo, unsteadiness of gait and faintness were increasingly frequent.

Through the courtesy of Dr. John McLean and with his assistance the flow of blood in the minute vessels of the patient's conjunctiva was studied with the biomicroscope. Considerable aggregation of the erythrocytes and slowing of the circulation were observed. Following application of a tube of ice water to the eyeball, the sludging of blood became excessive with segmentation of columns of blood and in some areas reversal of blood flow. These changes were evident for several minutes following withdrawal of the cold stimulus.

It seemed reasonable to believe that the more troublesome symptoms of the malady might be explained on the basis of the large amount of cold precipitable protein which was circulating in his blood; that cooling of skin capillaries might induce gelification with resultant obstruction of blood and that both the Raynaud's phenomena and the bleeding from his nose and gums might be consequent to such a mechanism. With these ideas in mind two measures were instituted with the hope of diminishing the amount of abnormal protein in the circulation.

Stilbamidine was administered because of its possible damaging effect on myeloma cells [49] which might be responsible for the elaboration of the cryoglobulin. Doses of stilbamidine dissolved in 5 per cent glucose in distilled water were given by slow intravenous infusion as follows: 50 mg. on March 16, 100 mg. on March 18, 150 mg. each day from March 19 to March 31 and from April 2 to April 5. During this period, while he received a total of 1.95 grams of the drug, he was kept on a diet free of animal protein.

No improvement could be noted during or after this therapy. The concentration of protein, while somewhat variable during the use of the drug, was not significantly reduced. The oozing of blood from the nose and gums continued and indeed became slightly more profuse. Headache, tinnitus, deafness and unsteadiness of gait were not alleviated.

Later attempts were made to reduce the concentration of cryoglobulin by partial exsanguination and blood replacement. In the 10 days from May 27 to June 4, 2,000 c.c. of blood were removed. On May 30, unusually severe bleeding from the gums over an eight-hour period resulted in additional loss of blood estimated as at least 500 c.c. A total of 3,000 c.c. of bank blood was given as replacement. At the end of the period the concentration of cryoglobulin was essentially unchanged. On June 5 and again on June 7, 500 c.c. of blood were withdrawn and replaced with an equal amount of bank blood. The concentration of cryoglobulin on June 10 was again unchanged. It may be significant, however, that on June 5 the previously incessant bleeding from the nose and gums stopped rather abruptly and did not recur for a period of 12 days. Interpretation of the relationship was complicated by the administration on June 2 of a vitamin C saturation test in which 100 grams of ascorbic acid had been given. In five hours this had resulted in an excretion of 267.6 mg. as compared with a normal excretion of at least 400 mg.

Further observations on the effect of exsanguination were made possible by excessive spontaneous hemorrhages. On August 2 bleeding from the bowel caused an estimated blood loss of 5,000 c.c. which was replaced by transfusions during a period

of two days. Again, on August 17 and thereafter for nine days hemorrhage from the bowel was so profuse that 6,800 c.c. of blood by transfusion were necessary to re-establish a hemoglobin level of 10 gm. Although observations on the concentration of the cold precipitable protein were not adequate during this period even these excessive hemorrhages resulted in no permanent reduction.

In table 2, the fluctuations in the level of total protein, albumin, globulin and cryoglobulin during the period of observation are presented in relation to the administration of stilbamidine and the induced and spontaneous loss of blood.

Following the last episode of rectal bleeding, epistaxes and oozing from the gums ceased for a period of more than a month. Deafness, tinnitus and blurring of vision continued without amelioration, but nutrition and general condition were notably improved.

TABLE II

Protein Values

Date	Total Protein Gm. %	Albumin Gm. %	Total Globulin Gm. %	Cryoglobulin Gm. %
3/4	13.0	3.7	8.3	6.3
3/15	15.2	4.2	11.0	8.9
3/16	Stilbamidine started			
3/18	15.6	3.7	11.9	9.8
3/24	11.0	2.7	8.3	6.3
4/5	Stilbamidine stopped			
4/6	12.1	3.6	8.5	6.7
4/7	12.8	2.8	10.8	8.9
4/26	10.5	3.5	7.0	4.9
5/26	11.1	2.8	8.3	5.8
5/27	Bleeding started			
6/2	11.0	3.2	7.8	6.1
6/7	Bleeding stopped—3,500 c.c. lost in 12 days			
6/10	10.6	2.9	7.7	6.5
8/2	Rectal bleeding—est. loss 5,000 c.c. in 2 days			
8/7	9.6	2.8	6.8	5.4
8/17	Rectal bleeding—est. loss 6,800 c.c. in 8 days			
10/20	12.1	3.0	9.1	6.8
12/21	Death—Heart blood examined post mortem			
	13.4	2.1	11.3	9.8

Bleeding from the nose and mouth began again on September 30 and melena was again apparent on October 7. The liver edge could be felt 5 cm. below the costal margin and the spleen was palpable. On October 13 hematuria appeared and rapidly became excessive. Urination was painful because of the passage of large filiform clots. Urinary output was not greatly diminished but the level of blood urea rose to 40 to 50 mg. per cent.

On October 31 he became almost totally deaf. Hemorrhages into his retina had increased gradually until he could no longer see. His deafness and blindness were the more distressing since his mental state remained alert and lucid. Although the hemorrhages from his urinary tract were large, it was decided that in view of his pathetic isolation, his weakness and discomfort, nothing further should be done to prolong his life. Three days before his death, his temperature which had remained within normal limits throughout his illness rose rapidly to 40° C., his respirations became labored and rapid; both lungs filled with coarse, bubbling râles. He died on December 17, 1948.

Postmortem Examination. The autopsy was performed and the report prepared by Dr. Devereaux H. Lippitt and Dr. Theodore Robertson of the Department of Pathology. *Diagnoses.* Plasma cell myeloma; mild bilateral interstitial nephritis;

septic infarct and pyelonephritis of left kidney; hemorrhage in terminal ileum; bronchopneumonia; healed right apical tuberculosis; hypertensive cardiovascular disease; cryoglobulinemia.

This last diagnosis was based on the demonstration of an abnormal eosinophilic coagulum in the myeloma cells, the bone marrow, the lumina of blood vessels and at sites of inflammation in other tissues and the assumption that this coagulum was a precipitate of the cryoglobulin which had been demonstrated clinically. Some of the more significant observations were recorded as follows.

Gross Examination. Weight 51 kg., height 160 cm. On palpation of the skull numerous nodular irregularities were felt. The entire length of each femur was filled with slightly pale, cellular gelatinous, red marrow. The marrow of the lumbar spine appeared slightly paler than usual. The *liver* projected 10.5 cm. below the xiphoid and weighed 1,960 grams. The *spleen* weighed 470 grams and was somewhat firm. *Lymph node* enlargement was minimal. The *heart* weighed 360 grams. The coronary arteries showed moderate atheromatous change. The *lungs* and *bronchi* presented the appearance of moderate generalized pulmonary edema with congestion in the costovertebral angle. In the right upper lobe there was a firm area of induration. The *kidneys* each weighed 170 grams. The thin capsules stripped with little difficulty leaving a cortex which was discolored by large, irregular, ecchymotic areas and many petechiae. The left renal pelvis was slightly dilated and there were many ecchymoses in the submucosa. The *small intestine* was not remarkable except for the last 30 to 40 cm. of the ileum. Here dark blood in the lumen had stained the serosa; the submucosa was intensely congested and in several areas small superficial ulcerations of the mucosa were noted.

Microscopic Examination. Bone marrow. Large numbers of myeloma cells were seen in the marrow of a vertebra, a rib and the right femur. The detail was best seen in the femoral marrow because it was not decalcified. The tissue was taken from the vicinity of an area of rarefaction. It was highly cellular and was almost entirely composed of myeloma cells. These were quite different from the plasma cells constituting part of the inflammatory exudates elsewhere in the body. They had oval, vesicular nuclei, eccentrically placed and containing irregular clumps of chromatin usually adjacent to the nuclear membrane. Occasionally seen within the nuclei were spherical, slightly basophilic, homogeneous nucleoli and a central clump of chromatin. Some of the nuclei were abnormal, and occasionally multinucleated cells were encountered. Their cytoplasm was variable in amount and appearance. Some of the cells had slightly basophilic, finely granular cytoplasm and a few displayed a perinuclear clear zone. Other cells showed large numbers of clear vacuoles which in some appeared to riddle the cytoplasm. Surrounding many of the vacuoles a peripheral crescent of eosinophilic colloid material could be seen. Between the myeloma cells there were fragmented cytoplasmic remnants and precipitated eosinophilic colloid material with staining properties identical to the intracellular crescents. Cellular elements of the erythroid and myeloid series were greatly diminished in number although foci of intense erythropoiesis were noted.

Spleen. About the cells of the red pulp there were small eosinophilic droplets; many hemosiderin-laden macrophages were scattered throughout the pulp. Only occasional myeloma cells were found in the sinusoids.

Lymph nodes. The lymph follicles of a retroperitoneal node were atrophic and without germinal centers. Scattered plasma cells and hemosiderin-laden macrophages were present. A left axillary node was largely replaced by fat. A rim of lymphoid tissue was composed mainly of lymphocytes and plasma cells.

Heart. In some areas the interstitial tissue contained small, precipitated eosinophilic globules.

Blood vessels. In the lumina of arteries, veins and capillaries throughout the

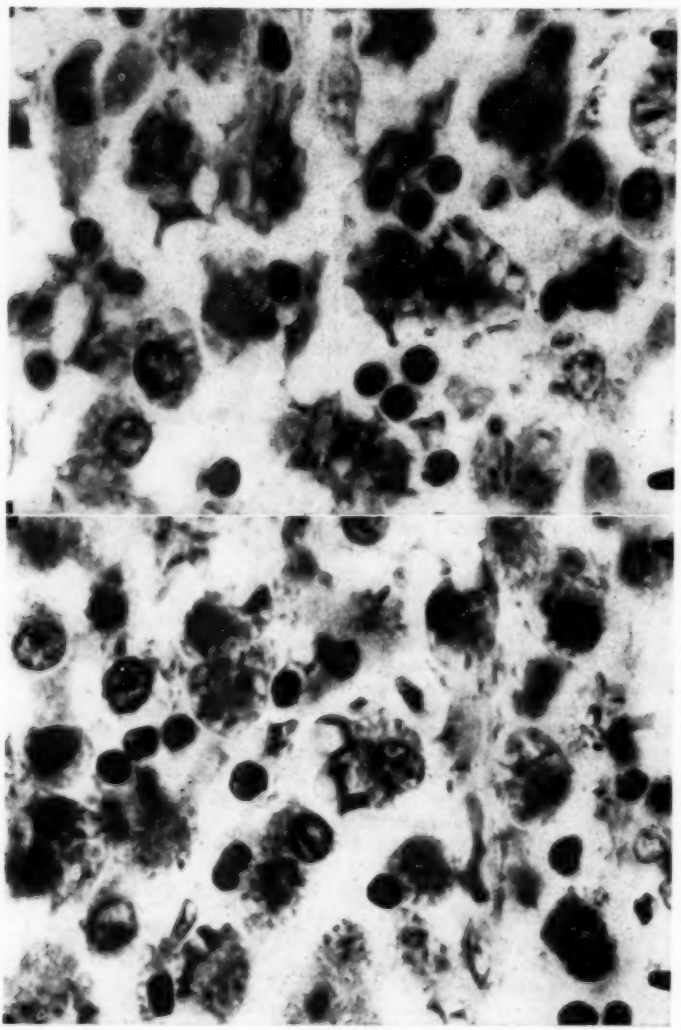

FIG. 2. Microphotographs of sections of bone marrow from case 2, × 1,260 stained with erythrosin-azure-methylene blue showing myeloma cells with extensive vacuolization and precipitated material in periphery of the vacuoles and outside of the cells in the marrow spaces.

body there was a deposit of material displaying the same eosinophilic stain as the precipitate in and about the myeloma cells. These formed in balls and sausage-shaped masses that appeared to enmesh and agglomerate the blood cells. Nowhere were there lesions which indicated that the precipitation had occurred ante mortem.

In view of the clinical history of Raynaud's phenomena and extensive disturbance of retinal circulation, the absence of thromboses in blood vessels was somewhat surprising. It is unfortunate, however, that the vessels of the extremities and other peripheral parts of the body were not examined.

Lungs. In the right lower lobe a large vein contained a recent thrombus in which there were masses of vacuolated eosinophilic coagulum mingled with the red cells. There was an acute purulent bronchopneumonic consolidation with destruction of alveolar and bronchial walls and engorgement of capillaries. In many of the alveolar spaces an eosinophilic coagulum was present. Many of the macrophages in the areas of inflammation were distended by large, clear vacuoles in their cytoplasm. The right upper lobe contained a firm mass made up of dense collagenous tissue which had replaced much of the parenchyma. This contained cartilage and several calcific nodules and was regarded as probable healed tuberculosis.

Kidney. In the left kidney there was a large area of coagulation necrosis involving both cortical and medullary tissue near the pelvis. This was circumscribed by dense polymorphonuclear cell infiltration and a fibrous wall. Giemsa stain showed clumps of cocci. The more peripheral renal parenchyma revealed marked interstitial nephritis with some associated glomerulitis and degeneration of tubules with colloid casts. In the right kidney there was no necrosis and the pelvis was not inflamed, but there was marked edema of the interstitium of the medulla. With high power, a fine granular eosinophilic precipitate similar to that in marrow and blood vessels could be distinguished in the edematous connective tissue. There was minimal interstitial nephritis.

Liver. Severe central necrosis was apparent histologically. The parenchymal cells of the central and occasionally of the midzonal portions of the lobules took an eosinophilic stain and exhibited pyknosis and dissolution of the nuclei. In several areas small necrotic foci of liver cells were surrounded by lymphocytes and plasma cells.

Special stains. A number of stains were used with only moderate success in an effort to determine the properties of the precipitated coagulum.

Cresyl violet, Congo red and the amyloid silver stain which were used for the detection of amyloid gave entirely negative results. Similarly treated cryoglobulin extracted from the serum also failed to give positive reactions.

Sudan IV staining of formalin fixed femoral marrow revealed very fine sudanophilic cytoplasmic stippling of a considerable number of myeloma cells. Precise localization of the substance in the cytoplasm was unsuccessful. No birefringent material was demonstrated.

For further delineation of the details of the myeloma cells, trial was made of Masson, erythrosin-azure-methylene blue and several separate components of these stains. None of the solutions colored the clear vacuoles. The most satisfactory staining was obtained with erythrosin-azure-methylene blue which colored the precipitated coagulum a bright red. When this was applied to a 1 per cent solution of cryoglobulin precipitated with Zenker's solution, the smeared granules stained red or when very dense a deep purple. With Masson the coagulum was deep red and the granules of cryoglobulin appeared in a variety of colors ranging from blue-green to deep purple and red. From these observations it was inferred but could not be proved that the precipitated coagulum and the cryoglobulin were one and the same.

Comment. The immediate cause of death in this patient appeared to be related to an acute, purulent bronchopneumonia and a septic infarct of the

kidney with pyelonephritis. The fundamental condition was multiple myeloma complicated by the presence of a cold precipitable globulin in uniquely large amounts.

Many of the manifestations of the condition may be attributed to multiple myeloma without reference to the influence of the cryoglobulin. Rouleaux formation of red blood cells, first mentioned in myeloma by Ellinger,[11] and later stressed by Reimann,[40] has been found in approximately 60 per cent of recently reported cases of myeloma.[1, 4] Autohemagglutination, with clumping of red blood cells in the diluting fluid of the pipette and in the counting chamber, has caused difficulty in obtaining accurate counts in many cases. Closely paralleling the rouleaux formation [13] is an increased sedimentation rate which is observable in a large number of cases and which may reach extremely high values. Increased viscosity has been frequently reported.[1]

All these phenomena appear to be related to hyperproteinemia and while there is no exact parallelism they are in general more marked when high globulin values and inversion of the albumin globulin ratio [13] can be demonstrated. They may be absent in myeloma in which no increase in protein is evident.

Hemorrhages are also frequent in patients with multiple myeloma. Adams, Alling and Lawrence [1] encountered them in 24 of their 61 cases. Epistaxis and bleeding from the gums are most common, but there are many records of melena, purpura and retinal hemorrhage. Delay in clot retraction has been noted and rarely thrombocytopenia has been encountered.[42, 44] In most instances, as in this case, platelet count, bleeding time, fibrinogen level and other tests indicative of a defective clotting mechanism have been within normal limits. The exact mechanism permitting the hemorrhages is not known but it has been the opinion of many students of the subject that it may depend upon sluggish circulation and capillary damage consequent to the hyperproteinemia.[4]

Anemia is one of the more constant accompaniments of multiple myeloma. It is apparent in many patients who have not suffered hemorrhage but in the absence of bleeding does not often become extreme.[1]

Other manifestations of this case which are accompaniments of multiple myeloma as such include enlarged spleen,[55] chronic renal damage,[8] and elevated level of uric acid in the blood [51, 16, 19] and which may have a significance similar to the high values of leukemia.

Pathologically the morphology of the plasma cells cannot be said to differ qualitatively from those encountered in typical cases of multiple myeloma in which the presence of cryoglobulin has not been suspected. Acidophilic inclusions in myeloma cells have been repeatedly described. Vacuolization is frequent and was observed sometimes in extreme degree in 29 of 51 cases of multiple myeloma reported by Bayrd and Heck.[4]

Features in this patient which are not often seen in multiple myeloma and may with some confidence be attributed to cryoglobulinemia are the

sensitivity to cold, the dilated superficial blood vessels, the mottling of the extremities, the extraordinary appearance suggestive of thrombosis in the retinal vessels, the sludging of blood in the conjunctival arterioles and capillaries, the tinnitus and deafness. Studies of the hanging drop of blood also disclosed the precipitate, presumably the cold precipitable protein which surrounded and enmeshed the agglutinated red blood cells and which readily disappeared when the slide was gently heated. It appears therefore that in addition to the rouleaux formation, the autoagglutination and increased viscosity characteristic of multiple myeloma, actual precipitation of cryoglobulin within the cooler and more exposed blood vessels might have contributed to defective circulation, injury of blood vessels and bleeding. Pathologically the principal characteristic which distinguished this case from the usual picture of multiple myeloma was the widespread acidophilic precipitate. In some of these respects it resembled closely the cases described by Hansen and Faber [20] and by Schumacher.[46]

Discussion

Clinical Characteristics of Cryoglobulinemia. The occurrence of cold precipitable proteins in the serum or plasma is not a very rare phenomenon. In most instances, however, they are present in minute amounts and unaccompanied by recognizable consequences. In reviewing the literature it is difficult to decide which instances of cryoglobulinemia are significant in constructing a clinical picture of the condition. There are, however, eight cases which have exhibited cryoglobulin in large or considerable amounts and have resembled clinically or pathologically one or the other of the two cases presented in this report. Some of their features have been arranged for comparative purposes in table 3.

Table III

Clinical Characteristics

Characteristics	P. I. Case 2	B. P. Case 1	Lerner and Watson	Wintrobe and Buell	Hansen and Faber	Flemberg and Lehmann	v. Bonsdorff, Groth and Packalen	Holmberg and Grönwall	Schwartz and Jager	Hill, Mulligan, Dunlop
Age and sex	58M	54M	56M	56F	48F	55	36M	40F	43M	55F
Multiple myeloma	Yes	?	No ?	Yes	Yes	Yes	Yes	No ?	No (Leukemia)	Yes
Cold sensitivity	Yes	Yes	Yes	Yes	Yes	Yes	No	?	Yes	Yes
Raynaud's syndrome	Yes	No	No	Yes	Yes	Yes	No	?	Yes	Yes
Purpura	No	Yes	Yes	Yes	Yes	Yes	No	?	No	No
Deafness	Yes	Yes	No	No	Yes	?	No	No	No	No
Retinal hemorrhage	Yes	Yes	No	Yes	Yes		No	No	No	No
Tendency to bleed	Yes	Yes	Yes	Yes	Yes	No	No	?	No	Yes
Anemia	Yes	No	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes
Renal involvement	Yes	No	Yes	No	Yes		No	?	No	No
Arthritis	No	Yes	No	No	No	No	Yes	Yes	No	Yes
Bence Jones protein	No	No	No	No	No		No	No	No	No
Rouleaux	Yes	No	No	?	Yes	Yes	Yes	?	?	?
Total protein	9.6–15.6	7.4	5.3	11.9	8.2	6.8	11.9	7.8	8.5	10.0–18.1
Albumin	2.1–4.2	3.9	3.5	2.5	4.0	3.7	4.3	4.3	4.1	1.8–2.1
Globulin	7.0–11.9	3.5	2.3	2.2	4.2	3.1	7.5	3.5	4.4	6.5–9.8
Cryoglobulin	4.9–9.8	0.02	0.8	7.2	2.2	1.3	?	?	?	?
Wassermann	Neg.	Neg.	Neg.	?	Neg.	?	Neg.	Atypical	Neg.	?

It will be seen that the diagnosis of multiple myeloma was definitely established in six of the 10 cases. In one the diagnosis was chronic lymphatic leukemia in which no evidence of plasma cell participation was discovered by appropriate examination in a most competent laboratory. Holmberg and Grönwall's case [23] was described with almost no clinical detail as a "chronic rheumatic infectious spondoarthritis." No evidence of multiple myeloma was disclosed by examination of the bone marrow or by roentgenograms of the skeleton although it was the opinion of the authors that their studies did not preclude the possibility of plasmacytoma. In the case of Lerner and Watson [28] no clinical or pathological examination of bone marrow was recorded and no evidence of myeloma or other cause of the protein was found at postmortem examination.

In those of the group who had multiple myeloma many of the symptoms can be attributed to that disease in which bleeding into the skin and many other organs, anemia, nephritis, rouleaux formation, autohemagglutination and increased sedimentation rate are frequent manifestations. As has been emphasized in the comment on our second patient, some of these symptoms may be related to hyperproteinemia. They are so frequently encountered, however, that they cannot be attributed to cryoglobulinemia which experience has shown is a relatively rare phenomenon in multiple myeloma. It is not unlikely, however, that the presence of cold precipitable globulin contributed significantly to the severity of the manifestations.

Symptoms which can perhaps be ascribed to cryoglobulin are the sensitivity to cold, the purpura and other dermatological manifestations that are induced by cold, the Raynaud's phenomena, the thrombotic appearance of retinal veins, the deafness, and possibly the arthritis. In passing, it is worthy of note that in none of the cases was Bence Jones protein detected in the urine and that the serum of only one of the cases displayed a false positive Wassermann reaction, a phenomenon not infrequently encountered in multiple myeloma.

Symptoms were induced by exposure to cold in eight of the 10 cases. In three, including our first patient, it appeared to be the exciting cause of a purpuric eruption. In the others it seemed to induce severe Raynaud's phenomena. In the report of von Bonsdorff's patient,[9] no mention is made of intolerance to cold, purpura or ischemia of the extremities although multiple, fleeting arthritis was a feature. Clinical history is lacking in the case of Holmberg and Grönwall.[23] Urticaria was induced by exposure to cold in Wintrobe and Buell's patient [57] and was noted without reference to cause by Schwartz and Jager [47] and Hill, Mulligan and Dunlop [21] as a symptom.

In addition to these 10 cases there are several in which the demonstration or quantitation of cold precipitable proteins was not complete but in which the symptomatology and clinical behavior were most suggestive of the presence of a cryoglobulin. Especially notable was the extraordinary case of Schumacher and Williams.[46] In its clinical and pathological aspects

it was in general typical of multiple myeloma. Bleeding occurred from the nose, rectum and vagina. Anemia and autoagglutination were prominent features. Intolerance to cold, Raynaud's phenomena and purpura were not mentioned. Especially remarkable was a total protein value of 23.27 grams per cent with albumin of only 1.63 and fibrinogen of 5.62 grams per cent. The chief reason for considering this case as a possible example of cryoglobulinemia was the observation of spontaneous coagulation of blood on exposure to air and the diffuse precipitation of protein in blood vessels and capillaries disclosed at autopsy in organs throughout the body. No studies of the effect of temperature on precipitation or coagulation were included in the record.

Foord's report [16] of four cases of multiple myeloma has attracted much attention in discussions of cryoglobulinemia. His paper at the time of its publication was perhaps chiefly useful in emphasizing autohemagglutination and rouleaux formation as diagnostic signs of plasmacytoma. Actually his patients present few signs which differentiate them from others with myeloma. In his first case intravascular clumping was noted in retinal veins when sufficient pressure was applied externally to slow the circulation in the eyeball. Large red granules were seen following one another along the course of the veins and resembling the aggregation seen in sedimentation tubes. Unfortunately this interesting observation cannot be interpreted because of the lack of controls. More impressive was the demonstration in two of his cases and in two which he later reported with Randall [17] of obstructive lesions consisting of inspissated protein in the glomerular capillaries. The significance of these observations is not clear. It seems unlikely that Foord was able to assemble four cases of cryoglobulinemia. His work suggests, however, the need of careful scrutiny of glomerular vessels in patients with hyperproteinemia.

In three other cases, the possibility of cryoglobulinemia has been suggested. Anderson and Samuelson's patient [2] complained of joint swelling and of cold hands and feet, which were designated as acrocyanosis. Vision was impaired and the appearance of the eyegrounds suggested multiple emboli and thrombi. The sedimentation rate was accelerated and the electrophoretic pattern indicated a great increase in gamma globulins. No observations were made concerning the effect of temperature on the behavior of the proteins. The presence of multiple myeloma or other cause of the hyperglobulinemia was not established.

Shapiro, Ross and Moore [48] encountered a viscid protein in a case of multiple myeloma which exhibited oozing of blood from the gums, bloody urine, purpura, hematomata and severe anemia. They were successful in isolating the protein and in determining its electrophoretic characteristics and molecular weight. In the sedimentation tubes clotting of supernatant serum was noted, but no record was made of cold precipitability. The viscidity of their protein as well as some of the clinical aspects of their case suggest but does not establish the presence of a cryoglobulin.

In one of Bing's [7] cases of hyperglobulinemia the serum was markedly viscous and after standing in the cold separated in two layers the lower of which froze into a white mass at 0° C. In describing this case Bing makes no mention of symptoms referable to exposure to cold.

The records of these few cases constitute the meager evidence concerning the manifestations which have been noted when relatively large amounts of cryoglobulin have been demonstrated in the circulating blood. The clinical significance of smaller concentrations is at present entirely a matter for conjecture.

Incidence of Cryoglobulinemia. While there is little reason to think that cryoglobulinemia is a common condition, there can be no doubt that most instances of its occurrence have escaped detection. The chance of missing its diagnosis is great since the protein may precipitate at room temperature. In all laboratories that follow the customary procedure of allowing red blood cells to settle in the ice box or on the laboratory bench, the abnormal substance may precipitate almost quantitatively, will fall with the blood cells and thus escape analysis in the supernatant serum. If perchance a small amount remains in the serum, it may be mistaken for a slight lipemia.

Wertheimer and Stein [56] reported cold precipitable proteins which they called "cold fraction" in four cases of endocarditis lenta, in two of nephrosis and in one each of Gaucher's disease, Niemann-Pick's disease and hepatic cirrhosis. Most impressive, however, was its occurrence in kala azar both in patients and in experimentally infected dogs. The phenomenon has also been encountered by Most and Lavietes [37] in approximately one-third of the active cases of kala azar which they encountered in American military personnel.

Lerner, Barnum and Watson,[26] in a study of 120 sera from as many individuals suffering from a variety of pathological conditions, observed spontaneous precipitation of protein from the cooled serum in 30 instances. In none of these was the amount large; a trace being reported in 18 and the remainder having a concentration ranging from 6 to 25 mg. per cent. They found none in any serum from 40 presumably normal individuals.

Preliminary observations have been made in our laboratory concerning the incidence of cryoglobulinemia among selected cases of a hospital population. Primary interest was centered upon multiple myeloma and Raynaud's syndrome. But the test was applied to all patients exhibiting hyperglobulinemia during the period of the study and to a considerable number of miscellaneous conditions. Alcoholics were included because at the time an investigation of the incidence of the sludging phenomenon in acute and chronic alcoholism was being carried out in the Department of Psychiatry. In all the bloods of 121 patients and 57 presumably normal individuals were subjected to analysis. The results are recorded in table 4.

In the table Grade II indicated a precipitate of approximately the same density as was encountered in our case of symptomatic purpura (22 mg. per

cent). Concentrations of this magnitude were found in 8 of the 121 patients. Among these were two cases of Raynaud's syndrome, one of which appeared in a case of pernicious anemia; one in typical Buerger's disease; one in a patient who had at the time of observation early syphilis, lymphogranuloma venereum and active tuberculosis; one in a curious case of chronic hepatitis, the precise nature of which was not determined; and finally in three cases of well-defined disseminated lupus. In addition to these more significant precipitates, traces of cold precipitable proteins were discovered in nine other patients. Tests of the normal sera were uniformly negative. It should be emphasized also that in only one case of multiple myeloma was even a trace of cryoprotein evident.

TABLE IV

Diagnosis	No. of Cases	Cold Precipitable Protein		
		Grade II	Trace	Negative
Multiple myeloma	14	0	1	13
Raynaud's syndrome	12	2	2	8
Buerger's disease	7	1	2	4
Lymphogranuloma	7	1	1	5
Chronic hepatitis	1	1	0	0
Hodgkin's disease	3	0	1	2
Pneumonia	2	0	1	1
Myocarditis	1	0	1	0
Disseminated lupus	6	3	0	3
Alcoholics	23	0	1	22
Miscellaneous disease	45	0	0	45
Total	121	8	10	103
Normal individuals	57	0	0	57

The possibility that cryoglobulins are constituents of normal serum in amounts so small as to escape chemical detection requires exploration. Reader and DeGara [39] made some preliminary observations with an anticryoglobulin serum which they prepared by immunization of rabbits against the protein of our case 2. They obtained negative results in cross testing with the sera of several supposedly normal individuals. Their observations as yet have been too small to permit conclusions. Furthermore their method could only disclose whether a normal serum was reactive to the particular cryoglobulin of case 2.

Nature of the Cryoglobulins. Cryoglobulins from only two patients have been satisfactorily characterized. The first was isolated by Lerner and Greenberg [27] from the case of cold sensitive purpura later reported by Lerner and Watson.[28] The second was from our patient with multiple myeloma and Raynaud's syndrome (case 2). It was studied by Miss Ella Russ who will report on its detailed analysis in a separate communication.[43] It appears that the two proteins are identical in ultraviolet absorption spectrum, isoionic point and electrophoretic mobility. Both are very viscid. Solubility characteristics in serum, dilute salt solution, water, alcohol and ammonium sul-

fate are similar but with minor differences. The total nitrogen content of the two proteins is approximately the same.

In spite of their relatively high molecular weight of about 190,000 and their somewhat uncharacteristic solubilities, both appear to be gamma globulins. In our case, the protein displayed homogeneity by electrophoresis and in the ultracentrifuge where it had a sedimentation constant similar to a gamma globulin. Furthermore analysis was made by Miss Ella Russ in the laboratory of Dr. E. J. Cohn by his microplasma fractionation technic on known amounts of our protein added to normal serum. It showed almost 100 per cent recovery of the cryoglobulin in the gamma fraction.

The close similarity or actual identity of the proteins in these two cases of quite different symptomatology is somewhat surprising and suggests the possibility that the same substance or very closely related substances might always be present when protein is found to precipitate spontaneously in the cold.

Chemical information concerning other cryoglobulins is meagre. Von Bonsdorff's protein [9] crystallized spontaneously when serum was allowed to stand at 8° C. It was relatively insoluble both in physiological saline and in distilled water although it was stated by the authors that washings of crystals with these solutions gave a strong protein reaction. Its molecular weight was approximately 200,000.

Holmberg's protein [23] also appeared as a crystalline precipitate although the crystals were not like those of von Bonsdorff. It was practically insoluble in physiological salt solution. Although its electrophoretic migration was almost identical to that of the protein of our case 2, its molecular weight as determined by ultracentrifugation appeared to be lower and the ultraviolet absorption led the authors to conclude that the substance was a pseudoglobulin.

Lerner, Barnum and Watson [26] examined the proteins from nine of their cases showing grade 2 cryoproteinemia. All but one of them dissolved when mixed in 0.9 per cent saline at 37° C. although none of the warmed solutions was completely clear. The ultraviolet absorption spectrum was determined in seven. In three the extinction coefficients at points of maximum and minimum absorption were identical and corresponded closely to that of the protein which had been characterized by Lerner and Greenberg. Two others gave absorption curves respectively similar to gamma globulins and fibrinogen. Two exhibited unusually high absorptions and one of these was said to be similar to the curve of a nucleoprotein.

We obtained no chemical data concerning the cryoproteins which we encountered in miscellaneous conditions. Reader and DeGara [39] tested the sera in three of them for precipitin reaction with the anticryoglobulin serum prepared from the protein of our case 2. In one, taken from a patient with syphilis, tuberculosis and lymphogranuloma venereum, there was a faint precipitin reaction. Tests on the others were negative.

Of great interest in relation to cryoproteinemia is the cold insoluble globulin described by Morrison, Edsall and Miller.[36] Their preliminary studies have indicated for this protein a molecular weight much greater than 190,000 and electrophoretic properties resembling a β_1 globulin. No exact data are available by which comparison can be made between our protein and I. R. Morrison's [35] contractinogen which Morrison, Edsall and Miller suggested might be identical with their cold insoluble globulin and which was said to precipitate on cooling and to redissolve when warmed.

In summary it may be said that some similarities are evident in the comparison of the cryoglobulin of case 2 and the cryoproteins encountered by others and ourselves. Striking differences are also apparent. Evidence at present indicates that a number of substances, not necessarily related, have in common the property of precipitability at temperatures between 37° and 0° C. In their specific reaction to temperature the family of cryoproteins may be regarded as somewhat analogous to the family of Bence Jones proteins.

Relation of Cryoglobulins to Cold Agglutinins. The manifestations of cryoglobulins and of cold auto- and isoagglutinins are sufficiently similar to suggest a possible close relationship. In sera possessing the property of cold agglutination there may be spontaneous clumping of red blood cells on exposure to cold and reversal by warming the blood to 20 to 30° C.[50] Clinically there is sensitiveness to cold which in some cases may result in acrocyanosis or severe Raynaud's phenomena.[32, 18] The possible confusion between the two conditions is well illustrated by the case of Schwartz and Jager [47] in which both a cold precipitable globulin and a cold auto- and isoagglutinin were demonstrated. Their study of these phenomena indicated that the property of cold agglutination was resident in the cryoglobulin itself since a solution of this substance in warm saline added to red blood cell suspension resulted in clumping of cells on exposure to cold and in disappearance of the clumps when the mixture was warmed to 37° C. The cold agglutination titers with this very dilute protein solution were only slightly less than the value of 1 : 1024 obtained with the whole serum of their patient.

Of interest also is the discovery by Rose [41] of the presence of cold agglutinins in two patients with kala azar. The possible relationship of this phenomenon to the cold precipitable proteins described by Wertheimer and Stein [58] and by Most and Lavietes [27] has not been investigated.

In several respects, these observations are quite opposite to our own. During the course of the study Luckey [31] was able to compare the behavior of the blood of our case 2 which contained large amounts of cryoglobulin with that of a patient whose cold agglutinin titer was 1 : 1,000,000 and whose serum contained no cryoglobulin. The agglomeration of cells in the serum containing cryoglobulin and no cold agglutinins could be classified as a pseudoagglutination and consisted of precipitation of protein with the appearance of red sand and the physical enmeshing of red blood cells. With

the serum containing cold agglutinins but no cryoglobulin there was diffuse clumping with no precipitate. In both instances the agglomeration could be dispelled by warming the slide to 37° C. A six-fold dilution of the blood containing cryoglobulin resulted, however, in a complete loss of the power to agglomerate red blood cells and to precipitate cryoglobulin from the solution. With very high dilution of the serum containing cold agglutinins the clumping was maintained.

It is of interest in this connection that von Bonsdorff [9] also found in his case that dilution of the serum to 1 : 16 resulted in complete disappearance of the autohemagglutination.

Origin and Disposal of Cryoglobulins. There is as yet no direct proof that plasma cells are the source of the abnormal proteins of multiple myeloma or of any other clinical or experimental condition. The idea that they may produce Bence Jones proteins was advanced long ago by Magnus-Levy [34] and many others.[29] Bing and Plum [6] were responsible for the thesis that all abnormal globulins may arise from plasma cells or their precursors. In reviewing the causes of hyperglobulinemia, they were impressed by the abundance of plasma cells which were manifest not only in myeloma but also in kala azar, lymphogranuloma venereum, Boeck's sarcoid, leprosy and other conditions. They suggested as a working hypothesis that "a comparison of the various affections in which hyperglobulinemia is found shows as a common feature an augmentation of plasma cells and other cells belonging to the reticulo-endothelial system within and outside the bone marrow."

This thesis has been repeatedly emphasized and extended [53, 54, 8, 28] and has been more recently elaborated to include the participation of plasma cells in the formation of immune globulins [12, 8, 10] and as a part of the mechanism of hyperimmunization in a variety of conditions.[52]

Some evidence that plasma or myeloma cells form the cold precipitable globulin in our own case 2 is offered by the concentration of acidophilic coagulum which we think is precipitated cryoglobulin in and about the myeloma cells in the marrow.

It seems not unlikely that some type or modification of plasma cells may have been the source of the cold precipitable protein in all of those cases in which multiple myeloma has been demonstrated. It is even possible that in Holmberg's case, where myeloma was not found, plasma cells could have been concentrated in areas that were not explored. The difficulty of applying the theory that plasma cells are always responsible becomes very great however, when one considers the protein in Schwartz and Jager's case [47] where the diagnosis was chronic lymphatic leukemia and where clinical and pathological study failed to reveal considerable plasma cell deposits. It is notable also that in the survey of Lerner, Watson and Barnum [26] cryoprotein was encountered in leukemia.

Whatever the source of the abnormal proteins of myeloma may be, the cells involved in their formation must be numerous or extraordinarily active to produce the daily excretion of 30 to 70 grams of Bence Jones protein which

has been observed in some cases.[23] Observations on the loss of blood in our case 2 indicated that phlebotomies and hemorrhage totalling 3500 c.c. in 12 days accomplished no reduction in the amount of circulating cryoglobulin. Even much larger hemorrhages caused only small and temporary lowering of the concentration. This seemed to indicate a large reserve in the tissues or a great capacity to produce the substance. The former hypothesis seemed untenable not only because of the molecular size of the protein which would pass with difficulty through capillary membranes but also because no large deposits of the acidophilic material could be found in tissues other than the bone marrow and the lumina of blood vessels. It seemed more probable that the organism was able to form the cryoglobulin rapidly and in large amounts.

During the 12 days in which 3500 c.c. of blood were lost, the plasma concentration of cryoglobulin averaged 6.2 grams. For maintenance of the level therefore, a production of approximately 20.0 grams per day was necessary. When one remembers that the bone marrow is a capacious organ [14] and that in this patient it was extensively infiltrated with, and in some areas replaced by myeloma cells, the rate of production does not necessarily exclude these elements as the source of the protein.

There is no information concerning the utilization and fate of the cryoglobulins. It may be stated with confidence that our patient was not excreting the protein in the urine except during the period late in the disease when there was active hemorrhage from the urinary tract. Repeated tests of the urine with the rabbit antiserum prepared by Reader and deGara were persistently negative. Its storage in large amounts in the tissues was not demonstrated. The possibility that it was metabolized or converted into other substances cannot be excluded. Of interest in this connection is the observation in case 2 that although the level of the protein fluctuated moderately with treatment and other circumstances, it never exceeded 9.8 grams per cent. The rate at which extra amounts appeared in response to hemorrhage might lead one to expect progressive increase in concentration. This may actually have occurred in the case of Hill, Mulligan and Dunlop [21] where, following transfusion, the level of total protein rose from 10.0 to 18.1 in a period of four days. The relative constancy of level observed in our case and in others in the literature may indicate some regulatory mechanism.

Significance of Cryoglobulinemia. The question of most practical interest in the study of these abnormal proteins is their relation to disease and abnormal function in the body. A summary of the observations indicates that they may be quite influential. Our cryoglobulin started to precipitate just below 37° C. and was grossly apparent at 34° C., a temperature well above that often attained in the extremities and other exposed parts of the body. Precipitation of the protein occurred immediately after withdrawal of blood. It enmeshed the red blood cells and caused the formation of a viscid gel which was resolved by heating but which grossly resembled clotting at temperatures below 37° C.

A priori reasoning would indicate that this phenomenon may occur within the body and may obstruct the flow through myriads of small vessels. Weight is given to this inference from the observed occurrence of Raynaud's phenomena, the appearance of sluggish blood flow with cyanosis, the injection of superficial vessels and the engorgement of retinal vessels and hemorrhages in the eyegrounds. The question may be asked whether this mechanism contributed to the profuse hemorrhages from nose, gums, bowel and urinary tract by producing stasis in blood vessels with subsequent minor injury of congested areas. Less inferential and more convincing was the actual observation of stasis and sludging in the conjunctival vessels and the exaggeration of the phenomenon with application of cold to the conjunctival surface. Of significance also is the story of these cases and of others in the literature that symptoms are exaggerated by exposure to cold. Indeed there can be little doubt that in the patients reported by Wintrobe, Hansen and Hill as well as in our own the presence of the abnormal protein was responsible for important symptoms, misery and death.

Although cases with large amounts of the cryoglobulin have been excessively rare, preliminary observations indicate that small concentrations of cryoprotein may be encountered quite frequently. Furthermore the observations on our case 1 and in the patient of Schwartz and Jager [47] suggest that even small amounts, such as 22 mg. per cent, may be quite significant. The occurrence of Raynaud's phenomena in patients who are known to have large amounts of cryoglobulin as well as the observation of lesser amounts of cryoprotein in cases exhibiting Raynaud's phenomena or even frank Buerger's disease suggests the possibility that the substance has been present but unrecognized in many patients with these conditions.

Summary

Record has been made of two patients in whom cold precipitable proteins were demonstrated in the blood and who developed symptoms probably attributable to their presence. In one, a case of multiple myeloma, the protein was obtained in pure form and was shown to be identical with the cryoglobulin described by Lerner and Greenberg and to have properties resembling a gamma globulin of high molecular weight.

Cryoproteins have been encountered most often in association with multiple myeloma but are rather infrequent members of the galaxy of abnormal proteins appearing in that disease. They have been reported in leukemia, arthritis, and in a high percentage of cases of kala azar. In traces they have been found in many miscellaneous conditions.

The demonstration of large amounts of cryoproteins has been rare but preliminary observations indicate that traces are not infrequent. Because they may settle with the blood cells when proteins are determined by routine laboratory methods, there can be little doubt that most instances of their occurrence have escaped detection.

The most prominent symptoms attributable to their presence are sensitivity to cold with Raynaud's syndrome or purpura and with a tendency to excessive bleeding from many mucous membranes. Other manifestations have been lesions of the retina which resemble extensive thrombosis, sludging of blood in conjunctival vessels, arthritis and progressive deafness. Examination of freshly drawn blood reveals extensive precipitation of protein. In the cases accompanying multiple myeloma there may be also many of the phenomena associated with the hyperproteinemia such as rouleaux formation, autohemagglutination, oozing of blood, anemia, and nephritis.

Cryoglobulinemia does not appear to be related to the phenomenon of cold auto- and isoagglutination although the clinical manifestations of the two conditions may be similar.

The source of the abnormal proteins has been discussed and morphological evidence has been presented that the cryoglobulin in one of our cases was formed by plasma cells.

Clinically cryoglobulinemia is significant chiefly because of its simulation of Raynaud's disease. Search for cold precipitable proteins should be made, however, in all cases of peripheral vascular disease, of multiple myeloma, symptomatic purpura, oozing or hemorrhages from mucous membranes without obvious cause and in all patients who present symptoms referable to exposure to cold. The extensive list of conditions in which, by preliminary observations, small amounts of cryoproteins have been demonstrated indicates the need for more complete survey and more detailed investigation.

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DURATION OF THE INFECTION IN SCARLET FEVER *

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In Illinois after the diagnosis of scarlet fever and other hemolytic streptococcal infections of the upper respiratory tract is made, "Isolation is required for a minimum period of 14 days after onset and thereafter until the nose, throat, glands, and ears are normal on inspection or until the physician reports complete clinical recovery." [1]

Other states have essentially the same regulation except that the minimum quarantine period is 21 days instead of 14. It is natural to assume that termination of quarantine marks the time at which the patient is no longer infectious and the time at which he has made a clinical recovery from his illness. Much evidence has accumulated showing that the first assumption is distinctly not warranted. Data to be presented here show that the second assumption likewise is not warranted, particularly since cultures of the nose and throat, urine examination, sedimentation rates, etc. are not required before lifting quarantine in scarlet fever.

In 1941 when the quarantine period for scarlet fever in Illinois was still four weeks it was shown [2] that 63 per cent of the patients still harbored hemolytic streptococci in the throat or nose at the time they were released and that many cases of scarlet fever were directly traceable to the return of the patient to a home in which there were susceptible persons.

To determine how long scarlet fever patients had some evidence of active infection a small follow-up clinic was established at Cook County Contagious Hospital. In accordance with the state law patients were released from the hospital 14 to 21 days after hospitalization if they had been free of fever several days and had no complication beyond mild cervical adenopathy. Cultures of the nose and throat on blood agar, routine urine examinations, and sedimentation rates by the Westergren method were made at the time of discharge. If cultures were positive or sedimentation rates elevated (and these two findings usually accompanied each other) the patient was asked to return a week later, at which time he was examined and the same tests repeated. Patients were asked to return at weekly intervals until the physical findings as well as these laboratory aids had established that clinical recovery was complete. In all, 163 patients were thus studied. Only half returned to the clinic and many of these stopped their return visits to the clinic before they were well. But even from the small group studied enough data were gathered to justify conclusions as to the general trend of the infection.

* Read at Sectional Meeting of American College of Physicians, Milwaukee, Wisconsin, November 15, 1947.

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TABLE I

Results of Throat Cultures in Entire Series Regardless of Treatment

	Positive for Hemolytic Streptococcus	Negative for Hemolytic Streptococcus
At time of discharge	78 (65%)	42 (35%)
1 Week after discharge	27 (54.9%)	24 (45.1%)
2 Weeks after discharge	28 (52.8%)	25 (47.2%)
3 Weeks after discharge	17 (41.5%)	24 (58.5%)
4 Weeks after discharge	10 (26.5%)	24 (73.5%)
5 Weeks after discharge	2 (20.0%)	8 (80.0%)
6 Weeks after discharge	3 (33.3%)	6 (66.7%)
7 Weeks after discharge	2 (25.0%)	6 (75.0%)
8 Weeks after discharge	2 (50.0%)	2 (50.0%)
9 Weeks after discharge	1 (50.0%)	1 (50.0%)

All but 24 of the group had specific treatment of some kind, but table 1 shows that 65 per cent of the patients still carried hemolytic streptococci in the throat, nose, or both, at the time of release from the hospital. Among those who returned to the clinic the incidence of carriers declined slowly week by week, but even after two months from the onset of illness some still harbored the organisms. At the time of discharge 75.2 per cent of the patients had elevated sedimentation rates and among those who returned for subsequent examination 72.2 per cent still had elevated rates one week later (table 2). The number who changed from elevated to normal rates each week continued to be about one fourth of those returning. Among those returning two months or more after the onset of illness 75 per cent or more still had elevated sedimentation rates.

TABLE II

Incidence of Elevated Sedimentation Rates among Convalescent Scarlet Fever Patients (Westergren Method)

	Percentage with Rates above 20 mm.
At time of discharge	75.2%
Percentage of those returning for examination with elevated sedimentation rates on subsequent examinations	
1 Week after discharge	72.2%
2 Weeks after discharge	66.6%
3 Weeks after discharge	77.7%
4 Weeks after discharge	54.5%
5 Weeks after discharge	60.0%
6 Weeks after discharge	100.0%
7 Weeks after discharge	75.0%
8 Weeks after discharge	75.0%

However, the most significant fact established was that approximately one third of the complications discovered became manifest *after* the patients left the hospital (table 4). Since only half the patients returned for follow-up examination it is almost certain that more complications occurred in the entire group than were recognized. Also worthy of mention is the fact that the more serious complications—including the two cases of rheumatic fever, one of nephritis and one of mastoiditis—developed after the patients

were discharged. It is probable that no two groups of clinicians would agree exactly on the incidence of complications. However, an effort was made to distinguish between cervical adenopathy and cervical adenitis of sufficient degree to be a cause of prolonged fever and disability. No otitis media except suppurative otitis is recorded. Joint pains and heart murmurs first recognized subsequent to the initial examination are recorded among the complications because they are clinical findings of potentially great

TABLE III

Average Sedimentation Rates (Westergren Method)
163 Patients

	Patients with Complications	Patients with No Complications	Entire Series
At time of discharge	70.0 mm.	36.5 mm.	60 mm.
1 Week after discharge	69.1 mm.	17.6 mm.	38 mm.
2 Weeks after discharge	53.6 mm.	30.8 mm.	35 mm.
3 Weeks after discharge	62.0 mm.	27.9 mm.	40 mm.
4 Weeks after discharge	42.0 mm.	22.4 mm.	29 mm.
5 Weeks after discharge	35.0 mm.	35.0 mm.	35 mm.
6 Weeks after discharge	45.2 mm.	25.7 mm.	40 mm.
7 Weeks after discharge	50.0 mm.	27.5 mm.	29 mm.
8 Weeks after discharge	62.0 mm.	15.0 mm.	38 mm.
9 Weeks after discharge	21.0 mm.	42.0 mm.	32 mm.

importance. In each instance they were accompanied by elevated sedimentation rates. However, rheumatic fever was diagnosed only in the two cases in which the disease was clearly established by continuing joint involvement and proved carditis. In our experience the diagnosis of rheumatic fever is often uncertain for several weeks and frequently is made in retrospect. Possibly some of these patients with mild joint pains and inconstant heart murmurs will subsequently be considered to have had rheumatic fever. It is worthy of note that the majority of the observations of joint pains and cardiac murmurs were made after the patient left the hospital.

TABLE IV

Complications Appearing in 163 Cases

	Total Number	Total Appearing after Discharge from Hospital
Purulent otitis media	8	1
Purulent rhinitis or sinusitis	7	3
Cervical adenitis	16	3
Joint pains	9	6
Heart murmurs not heard on admission	10	6
Rheumatic fever	2	2
Lobar pneumonia	1	1
Acute nephritis	1	1
Mastoiditis	1	1
	55 (33.7%)	24 (14.7%)

The patients were treated in a variety of ways. In the group listed in tables 5, 6, and 7 as being treated with "penicillin orally" treatment was with penicillin capsules containing 25,000 units per capsule administered every hour during the day and every two hours at night; penicillin lozenges containing 20,000 units held in the mouth and renewed every hour except at night; or a penicillin solution containing 1,000 units per cubic centimeter sprayed into each nostril and the throat every hour during the day and every three hours at night. While the local treatment was being given intensively it produced negative cultures for hemolytic streptococci but this effect was seldom found to last more than 48 hours after treatment was stopped. As seen in table 5 the ultimate effect was no better than when no specific treatment was given.

Convalescent serum was given promptly after the patients entered the hospital in doses of 20 cubic centimeters for small children and 40 cubic

TABLE V

Effect of Treatment on Cultures for Hemolytic Streptococcus

	Pen. I.M.	Pen. Oral	Sulfonamide	Conv. Serum and Sulfon.	Conv. Serum	No Specific Treatment
	(% of cultures positive for hemolytic streptococcus)					
Discharge	17%	79%	81%	82%	90%	71%
1 Week after discharge	31%	73%	58%	50%	100%	44%
2 Weeks after discharge	50%	57%	73%	50%	100%	38%
3 Weeks after discharge	50%	42%	54%	100%		30%
4 Weeks after discharge	25%	33%	20%	100%	75%	14%
5 Weeks after discharge		50%	50%			
6 Weeks after discharge		50%	40%			
7 Weeks after discharge			50%			
8 Weeks after discharge			67%			
9 Weeks after discharge			100%			

TABLE VI

Follow-Up Study

Effect of Treatment on Sedimentation Rates (Westergren Method)

	Pen. I.M.	Pen. Oral	Sulfonamide	Conv. Serum and Sulfon.	Conv. Serum	No Specific Treatment
	(Average sedimentation rates)					
No. of cases	33	31	48	14	13	24
Discharge	26.0 mm.	42.3 mm.	48.7 mm.	55.3 mm.	47.0 mm.	45.5 mm.
1 Week after discharge	22.9 mm.	50.6 mm.	42.3 mm.	39.0 mm.	42.0 mm.	34.7 mm.
2 Weeks after discharge	27.4 mm.	37.5 mm.	39.5 mm.	52.5 mm.	73.0 mm.	31.7 mm.
3 Weeks after discharge	41.3 mm.	29.5 mm.	53.5 mm.	41.0 mm.		35.2 mm.
4 Weeks after discharge	30.6 mm.	27.0 mm.	51.0 mm.	50.0 mm.	24.5 mm.	34.3 mm.
5 Weeks after discharge	20.0 mm.	18.0 mm.	45.0 mm.			
6 Weeks after discharge		37.0 mm.	45.8 mm.	41.0 mm.		
7 Weeks after discharge		10.0 mm.	41.1 mm.			
8 Weeks after discharge			33.0 mm.	82.0 mm.		
9 Weeks after discharge		42.0 mm.	21.0 mm.			

TABLE VII

Follow-Up Study

Complications at Discharge and Appearing after Discharge from Hospital

	Pen. I.M.	Pen. Oral	Sulfonamide	Conv. Serum and Sulfon.	Conv. Serum	No Specific Treat.	Total
No. of cases	33	31	48*	14	13	24	163
Cervical adenopathy	9	21	24	6	5	19	84
Cervical adenitis				1	1	1	3
Otitis media	1	2	1				4
Purulent rhinitis or sinusitis			3			1	4
Mastoiditis	1						1
Joint pains	1	1	3	1		3	9
Heart murmur (new)	2	2	2		1	2	9
Rheumatic fever		1				1	2

* One of these patients developed right lower lobar pneumonia with acute nephritis two weeks after discharge.

centimeters for older children and adults. This is not considered by the authors to be an adequate dose,[3] but this dose was all that could be given due to the meager supply of convalescent serum. The tables reveal that it had no appreciable effect in reducing the incidence of carriers of hemolytic streptococci, elevated sedimentation rates or complications. For this study we were unable to obtain a supply of scarlet fever antitoxin, which we would expect from past experience to be much more effective.

In the sulfonamide treated group sulfadiazine and sulfathiazole were used about equally in the usual dosage of 0.5 gram every four hours for young children and 1.0 gram every four hours for older children and adults. It will be seen that it too had little effect in producing "clinical recovery" and termination of the carrier state.

The control group, which received no sulfonamide, penicillin or convalescent serum, is a selected group, in the sense that only the milder cases were managed in this way.

The group treated with penicillin intramuscularly received 160,000 to 240,000 units per day divided into eight doses of 20,000 or 30,000 units each. Duration of treatment averaged six days. The record for termination of the carrier state and reducing sedimentation rates to normal is distinctly better in this group than in the others. These results correspond with those of other investigators.[4] Complications also occurred less frequently in the penicillin treated group than in the others. However, the one case of mastoiditis developing subsequent to discharge was in this group. It was in a child who had otitis media at the time treatment was instituted and the otitis had apparently cleared up at the time of discharge.

The various groups treated in different ways in this series of 163 cases are too small for sweeping conclusions, but the results presented would indicate that of the various measures used in treatment only penicillin intramuscularly in doses of 160,000 units or more per day had any demonstrable effect in terminating the infection.

Conclusions

It has been shown that the majority of patients with scarlet fever are still carriers of hemolytic streptococci when quarantine is terminated and for several weeks thereafter, and these patients frequently transmit the disease to other susceptible persons.

The majority of patients with scarlet fever have not completely recovered from the infection at the time the present quarantine is lifted; many complications occur after this time.

It would appear more logical to terminate quarantine of scarlet fever on the basis of negative cultures for hemolytic streptococci. Since many complications of scarlet fever, including rheumatic fever, occur several weeks after the onset the necessity for keeping patients with this disease at rest and under strict surveillance until their cultures no longer contain hemolytic streptococci and their sedimentation rates are normal is obvious.

In the present series only intramuscular penicillin in doses of 160,000 units per day or more and continued for an average of six days appeared to have any beneficial effect in changing the course of the disease and terminating the carrier state. However, no comparison with antitoxin is made since it was not used in this series, and the comparison with convalescent serum is not significant since it was used in inadequate doses.

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ELECTROKYMOGRAPHY—AN APPRAISAL OF ITS PRESENT CLINICAL STATUS*

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In essence, electrokymography is a method of recording the repeated pulsating motions exhibited by the heart and great vessels. A photosensitive tube is used to pick up variations in the light emitted by a fluoroscopic screen placed over the border of the cardiovascular stripe.

The device, in its present form, was originally developed during the war years with the hope of obtaining an apparatus which might be applicable to mass screening technics in the investigation of heart disease. Although many individuals contributed ideas and suggestions for its development, Drs. B. R. Boone, G. C. Henny, and W. Edward Chamberlain are among those primarily responsible for the present development of the apparatus reported on in this paper.[1, 2] Earlier work by Hjelmare,[3] Heckmann [4] and others has been reviewed by Luisada et al.[5] The history of the development of roentgenkymography, parent of electrokymography, is well known.

The electrokymograph describes with some detail the motions undergone by the borders of the heart and great vessels. A photoelectric pick up tube is mounted behind a small square bit of fluoroscopic screen in a cylindrical metal housing. A small slot in the housing, 5 by 20 mm., admits roentgen-rays to the bit of screen. This pick up unit is mounted on the patient's side of the roentgenoscope screen so that it can be centered and swiveled about. Current produced by the tube is conducted through a filter box which removes the roentgen-ray ripple, then to the lead terminals of a standard recording string galvanometer. A separate power source supplies the phototube. A schematic representation of the apparatus is presented in figure 1. By means of this device clear records without ripple or significant true signal distortion are obtained, as stated by Henny et al. in their detailed description of the apparatus.[1, 2] As a timing device for the kymographic tracing, a mechanical carotid pulse recorder is used. A small cup pick up is connected by a rubber tube to a rubber tambour and pointer mounted within the galvanometer lens tube. The mounting of the recording tambour is so adjusted that pointer position and excursion can be readily controlled. Other methods of timing, such as the phonocardiograph or the electrocardiograph, can readily be used, but have minor practical disadvantages for routine use. Luisada et al.[5] have used the phonocardiograph as a timing device, calling the method fluorocardiography.

The roentgenoscope may be run at standard milliampere and kilovolt settings. We have been able to obtain satisfactory tracings in most patients

* Received for publication September 9, 1948.

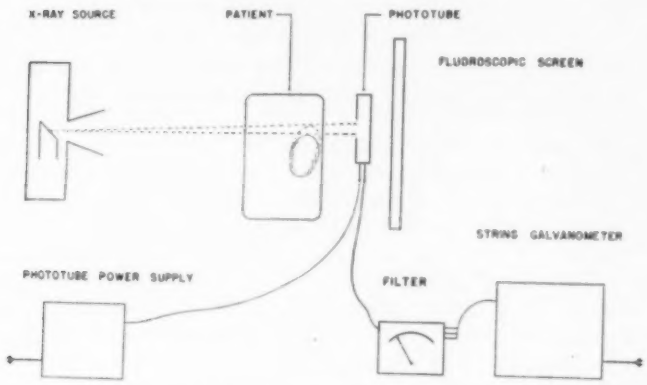

FIG. 1. Schematic representation of apparatus.

with as little as 2 to 3 ma., and 85 kv., and 10 R or less per minute incident upon a small, changing skin area.

The string galvanometer recorder can be run at standard sensitivity and film speed with quite satisfactory results when using the carotid pulse as a timing device. Where the phonocardiogram is used as a timer, faster film speeds are necessary.

In practice, the patient is placed before the roentgenoscope in the standing or sitting position. Records can be made with the patient recumbent, but in this position oblique views cannot be easily obtained. The carotid pulse cup is attached, the roentgenoscope turned on, and the photoelectric pick up aligned. The outline of the slit in the pick up tube housing is placed half way over the border of the cardiac silhouette, and in such a position that the long axis of the slit is approximately perpendicular to the edge of the cardiovascular silhouette in the region desired (figure 2). The central point of the slit should correspond roughly to the central beam of the roentgenoscope. After placement of the phototube, the roentgenoscope shutters are closed down as far as the border of the outline of the phototube housing, and

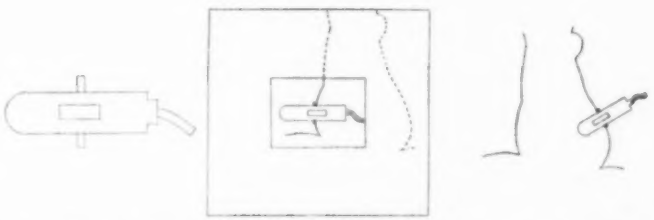

FIG. 2. Illustrating placement of the phototube. Note side projections on tube housing for positioning.

just before recording is begun the patient is asked to hold his breath. Care should be used to avoid production of a Valsalva or Müller effect which will distort the tracing. When satisfactory pulsations are seen on the galvanometer screen after adjustment, the camera is started and about 10 cardiac cycles are recorded.

Generally, at least 10 recordings of various portions of the silhouette can be taken in 5 or 6 minutes, with the patient receiving an average total exposure of from 50 to 100 R limited to a small skin area. Erythema was never noted even after tracings had been made on two or three occasions within a period of a few days. Measurements of operator exposure have been well within so-called safe limits, even with daily use of the apparatus.

A present defect of the apparatus is the lack of any method of wave amplitude standardization. The filter box of the apparatus is equipped with a rheostat control which allows adjustment of wave height to the confines of the recording film, and this rheostat setting usually must be changed with every view recorded. Even with approximate identical settings on different views of the same heart, the wave amplitudes are only roughly comparable.

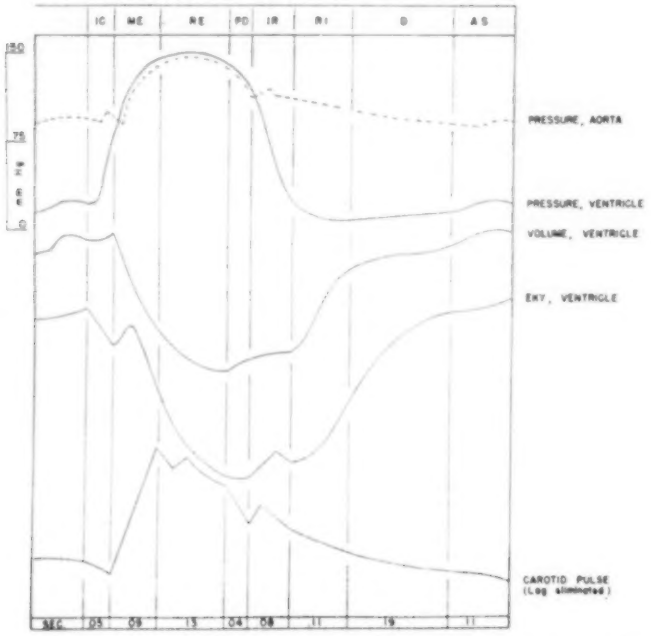

FIG. 3. *Systole:* IC—isometric contraction; ME—maximum ejection; RE—reduced ejection. *Diastole:* PD—protodiastole; IR—isometric relaxation; RI—rapid inflow; D—diastasis; AS—atrial systole.

This lack of standardization is not easily overcome, since many factors, including positional, volumetric, and density changes, are involved.

As compared with the roentgenkymogram, which shows the outline of the heart and great vessels, together with wave forms representing pulsations occurring in multiple areas, the electrokymogram records the motion occurring at a single area at one time, without even relative comparison possible between the amplitude of pulsation at different points in the silhouette. The great advantages of the electrokymogram are that a clear large wave form is obtained, coupled with a more precise timing device, which much more often permits ready, sharp identification and differentiation of the events occurring during various phases of the cardiac cycle. With more elaborate apparatus the motions of several areas can be described simultaneously, or multiple channel recording of cardiac cycle events as reproduced by various means can be performed.

A representation of cardiac cycle events is reproduced in figure 3. As Boone et al.[6] have pointed out, the similarities between the ventricular volume curve and the electrokymogram of the ventricle are striking, and may be due to a number of factors. When the phototube slot is placed entirely within the cardiac shadow, a cycle continues to be recorded, and if the slot is placed over lung tissue, a cycle may also be recorded. From this it can be seen that shadow density is one of these factors. Other important determinants of wave form are volumetric changes and positional changes. Examples of positional changes are the tendency of the apex towards "pendulum" motion, the motion of the apex towards the base with septal contraction, the "wringing" motion of the ventricular musculature, and the change in outline which may occur during isometric contraction or isometric relaxation. Any motion of the patient, movement of the phototube, or movement of the fluoroscopic screen to which the phototube is attached, will introduce artefacts into the tracing. Apparently the final tracing is a summation of these movements, the volumetric changes principally determining the final wave form.[6]

These waves have a characteristic form for each of the various chambers or segments of the heart and great vessels, with minor variations depending upon the angle of view or rotation at which the tracings are taken. Figures 4 and 5 are illustrative. Polarity is so arranged that a downward excursion represents a motion towards the midline, or a decrease in density; an upward excursion, the converse. It is immediately apparent that arterial curves resemble the carotid pulse in form and timing, while the ventricular curves are opposite in form. At the apex, the ventricular curves tend to show a small outward peak early in systole (X peak) and often have a V-shaped bottom where systole ends, without any indication of the end of the isometric relaxation phase. Progressing upwards along the left cardiac border from the apex towards the base, the X peak tends to disappear and the V-bottom is replaced by a W-shaped bottom indicating the beginning and end of the isometric relaxation phase.[10] Right ventricular curves resemble those of the

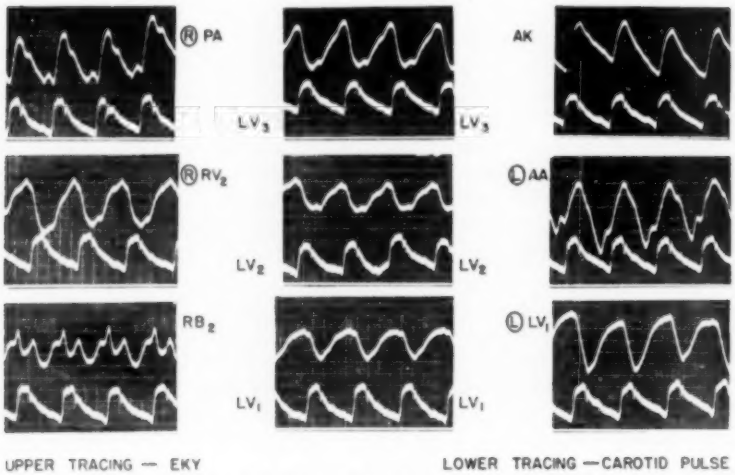

FIG. 4. Case 33, S. H. Smallest timing lines at 0.04 second intervals. Illustrates characteristic wave forms of various portions of the heart. R in circle—R.A.O. L in circle—L.A.O.

left ventricle, while curves obtained over the auricles are composite forms. Over the right auricle in the A–P view, for instance, predominantly arterial or predominantly ventricular curves may be obtained, depending upon whether one records a tracing high or low along this border. Curves recorded higher up, nearer the base of the ascending aorta, will be predominantly arterial, while those recorded lower down, near the juncture between the auricle and inferior vena cava, will be predominantly ventricular as the auricle is passively influenced by movements of the right ventricle. In a similar fashion, views over the upper left border of the heart, below the

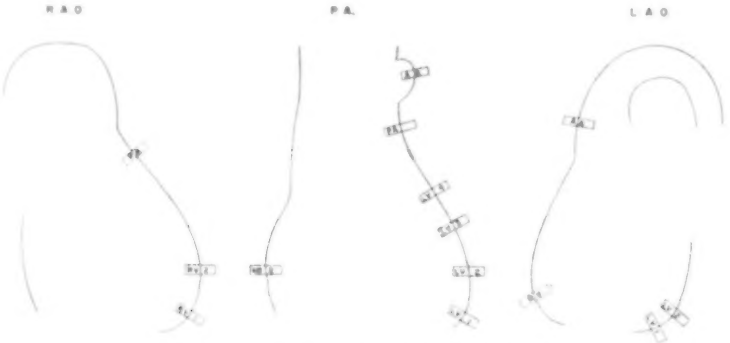

FIG. 5. Illustrating views taken in routine use.

aortic knob, in the P–A view, may be mixtures of the movements exhibited by the left ventricle, left auricle, and pulmonary artery. The pulmonary artery tracings generally show a slower rise during the beginning of ejection and have a more prominent incisura than tracings from the aorta.

These considerations, and similar ones, dictated our choice of the areas shown in figure 5 as those to be used for routine work. Tracings from many more areas than these can be taken, and often are desirable in particular cases. One should, however, be familiar with cardiac anatomy, and take care not to confuse areas. After a little experience, the location from which the tracing at which one is looking was taken can be told at a glance, particularly on those records taken from normal individuals. This feature may be of definite assistance in the determination and localization of questionable border areas of the cardiovascular stripe.

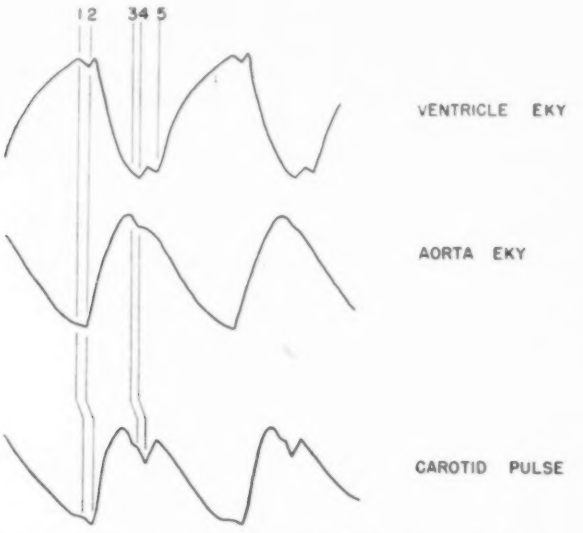

FIG. 6. Basis for interpretation, schematic. Explanation in text (after Boone et al.).

In figure 6 a schematic basis for the identification of the various phases of the heart cycle, as recorded by the electrokymograph, is presented. The recording of the carotid pulse is not simultaneous with the recording of the electrokymogram, the lag factor being due to the transmission time of the impulse from the ventricle to the point of pick-up on the carotid pulse in the neck and to the transmission of the impulse from the point of pick-up on the neck to the recording pointer. This latter factor is consistently about 0.01 second when the length of the rubber hose in the carotid pulse air conduction system is about 6 feet in length.[7] In practice it is convenient to

measure the time from the indication of beginning ejection on the ascending aorta electrokymogram to the indication of beginning ejection on the simultaneously recorded carotid pulse, and use this as an estimation of the constant lag time of that individual, adding about 0.01 to 0.03 second to this figure for the left ventricular and left auricular kymograms to obtain the total lag. In determining lag on right ventricular and auricular kymograms, the degree of left and right ventricular asynchronism must be determined in addition [8, 9] and the amount of lag then calculated.

When the carotid pulse is used as a timing device for the electrokymogram, four readily distinguishable points on the carotid pulse tracing may be used as indicators of phases of the cardiac cycle. In figure 6, point 1 represents the beginning of the isometric contraction phase; point 2 the end of isometric contraction and the beginning of systolic ejection; point 3 the beginning of protodiastole; and point 4 the end of protodiastole and the beginning of the isometric relaxation phase. Point 5 represents the end of the isometric relaxation period on the ventricular electrokymogram.[10] On ventricular curves, points 2, 4, and 5 nearly always coincide with some change in direction or slope of the wave form, while point 3 is almost never distinguishable. On arterial curves, points 2 and 4 usually may be distinguished by changes in direction or slope.

Electrokymographic tracings show a considerable range of variation in normal subjects. As a consequence of the paucity of data with regard to what is normal and what is not, interpretation is uncertain. Different observers may vary as to the overall significance of an abnormal tracing, while agreeing on minor points. The same observer may have entirely different opinions as to the significance of a set of tracings on different days. One of the reasons for the variation in interpretation is insufficient knowledge of what constitutes the normal and abnormal, and the range of normal variation. Lack of wave amplitude standardization is another hindrance to interpretation.

The electrokymogram, then, reproduces motions of the heart and great vessels with accuracy. It is coupled with a fairly precise timing device which permits identification of certain phases of the cardiac cycle as recorded. It may aid in identification and localization of unknown or questionable areas of the cardiovascular stripe, and as compared with the electrocardiograph, reproduces the mechanical events, rather than the electrical events, of the cardiac cycle. The disadvantages of the device are the expensive equipment and trained personnel required for operation; the small area recorded at one time, making multiple views necessary; and the lack of standardization. It is a laboratory procedure. In evaluating the tracings one is confined to consideration of wave form and timing relationships.

In studying individuals with abnormal hearts by means of the electrokymograph, one is confined, then, to the study of wave form and timing relationships. The literature on roentgenkymography is extensive, and contains considerable pertinent data on these factors as recorded by the roent-

genkymographic apparatus. With modifications and exceptions, these data have formed the basis of judgment in evaluating abnormal electrokymographic tracings. As more has been learned, constant revision of criteria has occurred, but still there is much to be learned. As Hirsch [13] has stated, variations of wave form from the normal may be due to (1) disturbance of rhythm; (2) intrinsic muscle changes; (3) extracardiac influences, modified anatomic relationships of the heart, and intrathoracic pressure changes; and (4) valvular defects. In 1936 Scott and Moore [11] suggested that the changes in heart muscle which produced changes in the electrocardiographic tracing indicative of myocardial damage, should produce recognizable changes in the roentgenkymogram. Later, in 1941, Scott [12] used the roentgenkymogram to estimate grossly the extent of myocardial damage. These writers, and others,[13, 14] discussed the clinical applications of roentgenkymography and described abnormal wave forms.

In evaluating the tracings in the present study, routine measurements of the cycle length and systolic ejection duration, as measured on the electrokymogram, were made and the relationship of duration of systolic ejection to cycle length for the left ventricle was determined. This relationship was compared with measurements obtained from the electrokymographic tracings of 181 normal subjects by Drs. R. B. Boone, and E. F. Randak, and kindly supplied to the authors by them. The measurements obtained from the normal subjects appeared to make a rough curve, systolic ejection being prolonged with increased cycle length. As is well known, digitalis tends to shorten systolic ejection duration, but measurements so far have not shown any correlation between etiologic types of heart disease and the ejection-cycle length ratio. Marked deviations from "normal" ranges were taken as one indication of abnormality. Since it is probable that the range of normal will be extended with further experience, detailed measurements will not be presented.

PAc time, and the duration of the isometric relaxation phase of the cardiac cycle, as measured on the electrokymogram, were also estimated. PAc time, as Chamberlain et al.[8] and Ellinger et al.[9] have shown, is a measure of ventricular asynchronism, and for practical purposes is diagnostic of bundle branch block. The PAc time is the time interval between the indication of ejection on the pulmonary artery electrokymogram and the indication of ejection on the simultaneously recorded carotid sphygmogram, representing right and left ventricular events, respectively. When ejection on the pulmonary artery occurs first, a plus sign is used to prefix the time interval, and when ejection on the pulmonary artery comes after the indication of ejection on the carotid, a minus sign prefixes the time interval. Thus a PAc time of more than plus 0.04 second indicates that the right ventricle is leading to an abnormal degree, and that a left bundle branch block exists; while a PAc time of more than minus 0.02 second indicates that the left ventricle is leading to an abnormal extent and that a right bundle branch block exists.[9] Figure 7 illustrates a right bundle branch block; figure 8 a

left bundle branch block. Unfortunately, however, a clean-cut indication of ejection on the pulmonary artery is not always obtained as positional variations may occur at this time.

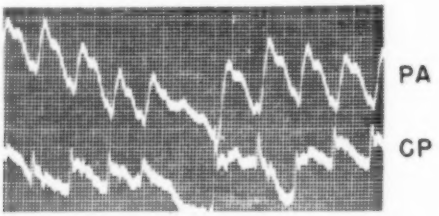

FIG. 7. Right bundle branch block. Note artefact caused by patient's motion.

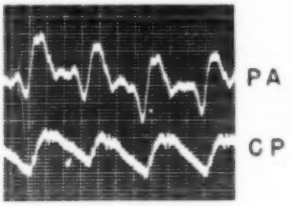

FIG. 8. Left bundle branch block.

Boone and Randak [19] have advanced evidence for the identification of the isometric relaxation phase, or I. R., on the electrokymographic tracing, and suggest that the duration of this phase of the cardiac cycle may be a criterion of the condition of the cardiac musculature. Figure 9 illustrates a prolonged

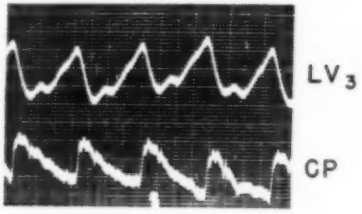

FIG. 9. Illustrating prolonged I.R.

I. R. They found that the I. R. duration, in normal subjects, appeared to be independent of age, sex, pulse rate, or blood pressure; and that 68 per cent of normal subjects had I. R. durations between 0.10 and 0.13 second, while 71 per cent of 47 cases with heart disease had I. R. durations between 0.15 and 0.18 second.

To complete the evaluation of each set of tracings, the apparent rhythm was noted, and the wave contour of the left and right ventricles, right auricle, pulmonary artery, and aorta were studied.

The general purpose of the study, in addition to an appraisal of the apparatus as a clinical tool, was to discover if etiologic types, or patterns, of heart disease could be found by this means. The results have been disappointing to date, but continued work may well give more substantial results.

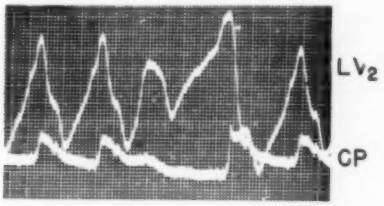

FIG. 10. Illustrating diastolic collapse curve and an extrasystole.

Determination of the cardiac mechanism from study of the electrokymogram is, at best, an approximation, since only a single area is recorded at one time; ordinarily there is no simultaneous recording of auricular and ventricular events; and the events recorded are mechanical rather than electrical ones. Auricular tracings are difficult to evaluate, and the motion of auricular contraction may be hidden or not well represented. Sinus rhythm is suspected if the cycles are regular, at a normal rate, and if normal auricular tracings are obtained. Ectopic beats are well demonstrated and if a good

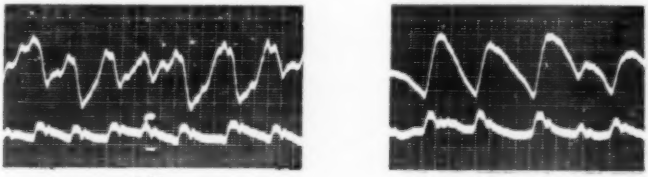

FIG. 11. Auricular fibrillation.

auricular tracing of an extrasystole is obtained which shows a dropped "A" wave (the "A" wave representing auricular contraction) one may believe, if the extrasystoles originate in a constant ectopic focus, that the extrasystoles are ventricular in origin. Figure 10 illustrates an extrasystole on the left ventricle. Auricular fibrillation is easily spotted by the irregularity and varying amplitude of the wave forms from cycle to cycle. Auricular flutter generally produces satisfactory "A" waves which are quite striking as evi-

dence of mechanical motion following rapid electrical phenomena. Figure 12 is a striking illustration, taken from the LV_1, LV_4, RB, and PA positions of a patient with auricular flutter, complete A–V dissociation, and idioventricular rhythm. The slow ventricular rate with regular, rapid "A" waves coming without constant relationship to the ventricular component (large downward excursion) of the curve leads one to suspect flutter and complete atrioventricular block. In this case an additional clue is the prolonged PAc time, pointing to a bundle branch block pattern and an ectopic focus as the ventricular pacemaker. Lesser degrees of A–V block are not well demonstrated. Bundle branch block is well demonstrated, as has been discussed above. We have had little experience with electrokymography in cases of paroxysmal tachycardia, but it appears that exact rhythm determination is not possible, although the regularity, rapid rate, and absence of flutter waves might be suspicious of this mechanism. Mechanical alternans is, as might be expected, well demonstrated, and has been discovered occasionally where clinically unsuspected. Insofar as mechanism disturbances are concerned, it would appear that the electrokymogram is seldom diagnostic, as the electrocardiogram nearly always is.

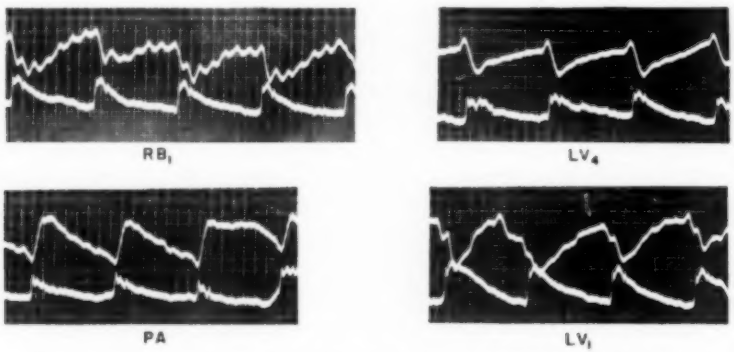

FIG. 12. Tracings from a patient with auricular flutter and complete A–V dissociation. Note small flutter waves in RB_1 position.

While it appears probable that intrinsic muscle changes may cause deviation of wave form from the normal, much work on this subject remains to be done. Individuals without apparent rhythm disturbances, abnormal extracardial influences, or apparent valvular defects do show definitely abnormal wave forms. Many of these are individuals who present evidence of having had a myocardial infarction, recent or remote, but a few individuals who show localized wave form abnormalities do not. It is interesting to speculate as to the percentage of these individuals who have had small, localized, unrecognized infarctions.

As several writers have suggested, the duration of the isometric relaxation period, as measured on the electrokymogram, may be a criterion of the state of the ventricular musculature. There appears to be a considerable overlap, so that it is often difficult to determine in the individual instance whether or not the I. R. duration is normal. Of the patients with abnormal hearts in this series, 69 per cent had I. R. durations ranging from 0.13 to 0.18 second. Prolongation of the I. R. appears to occur most often in hypertensive heart disease.

Several types of ventricular wave forms have been described by roentgenkymographers as being associated with myocardial infarction or localized areas of fibrosis, in addition to the fact that diminution or absence of pulsations in a localized area over the left ventricular border was frequently found. These forms might be called (1) systolic expansion, or arterial pulsation; (2) systolic plateau, without significant inward motion during systole; (3)

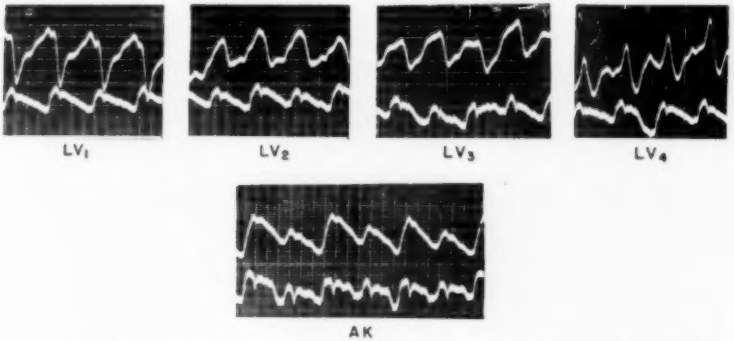

FIG. 13. Systolic expansion curves and systolic plateau curve from left ventricle of individual with coronary heart disease. Note pulsus alternans shown in AK position.

peaked waves with "shouldering" during terminal systole and with diastolic collapse; and (4) diastolic splintering. Examples of 1 and 2 may be found in figure 13. Figure 10 shows a diastolic collapse curve. Diastolic splintering is rarely seen in the electrokymogram. There is little doubt about the abnormality of wave forms 1 and 2 when seen in a ventricular area. The diastolic collapse curve is, however, seen in normal individuals, although it appears to be a smooth curve with little splintering in normals; while in cases with pathologic lesions, the diastolic collapse appears to represent 50 per cent or more of the total wave amplitude. In normal individuals a typical normal curve is usually found elsewhere on the ventricle.[15] This type of curve seems to be most often associated, in abnormal cases, with coronary heart disease. Speculation as to the cause of this type of wave form is interesting. It may represent a weakened myocardium unable to maintain high intraventricular ejection pressure, so that the aortic valve closes while

some fibers are still contracting, and inward diastolic movement occurs; or a partially damaged area into which blood is forced during systole, but which retains sufficient elasticity to force its contents into the cavity of the ventricle during early diastole.

Although it is in the study of myocardial infarction that the electrokymograph might seem to give the most concrete immediate results, here also results are often equivocal. Of six cases of posterior and basal myocardial infarction, only one kymogram was judged compatible with the diagnosis. Of 13 cases of anterior and apical infarction, seven were judged compatible with the diagnosis. It is interesting to note that three instances of "cardiac aneurysm" or localized systolic expansion over the ventricle, were found in patients in whom serious heart disease was unsuspected. Too few cases of infarction have been studied to warrant comment here upon the correlation of the electrokymogram with severity of attack, degree of recovery, or electrocardiographic changes, as has been done by Sussman et al.,[16] for the roentgenkymogram.

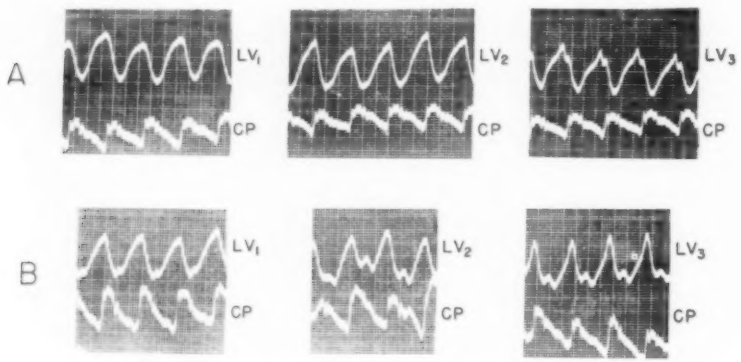

FIG. 14. A. V bottom curves. B. Normal W bottom curves.

Valvular defects may produce early or delayed ventricular filling, increased auricular distention, accelerated auricular filling during systole, or early or delayed aortic ejection, as may be realized from consideration of the dynamics involved. These cardiac abnormalities may be present, and yet apparently produce no recognizable change from the normal in the electrokymogram. Although it might be expected, for instance, that a mitral or aortic insufficiency would alter the normal configuration of the isometric relaxation period, as measured on the electrokymogram, this may not occur. In addition, normal individuals may sometimes show patterns which are produced ordinarily by valvular disease. Apparently the defect must be large before variations appear which may be recognized as abnormal by the observer.

Three apparent patterns of ventricular wave forms may be produced by mitral or aortic valvular insufficiency. The first of these, illustrated in figure 14, the "V bottom" curve, or ventricular curve without a discernible, definite isometric relaxation period being evident, must occur over all the left ventricular border in the P–A view before it has significance, and even then normal individuals may show this type of curve. In the second type the onset of the isometric relaxation period on the left ventricle electrokymogram comes after (by at least 0.04 second) indication of aortic valve closure on the carotid pulse tracing with lag eliminated. This type of curve is associated with mitral insufficiency. It is suggested that the discrepancy is due to terminal mitral regurgitation after aortic valve closure. Figure 15 A illustrates this second pattern. The third pattern shows the onset of isometric relaxation on the electrokymogram of the left ventricle coming before

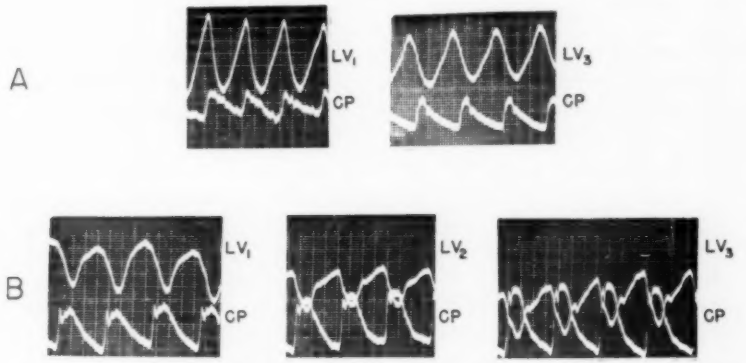

FIG. 15. A. Illustrating discrepancy in the indication of onset of the isometric relaxation phase in mitral insufficiency. B. Illustrating discrepancy in the indication of onset of the isometric relaxation phase in aortic insufficiency.

(by at least 0.04 second) the carotid pulse indication of aortic valve closure. This third pattern occurs in aortic insufficiency, and it is suggested that the discrepancy is due to delayed, imperfect aortic valve closure. Figure 15 B illustrates this pattern. In addition, cases of aortic insufficiency may show aortic tracings with a quick systolic rise and rounded, smoothed curves.

We have had little experience with electrokymography in congenital heart disease, pericardial effusion, aneurysms, or other conditions which produce greatly modified anatomical relationships or intrathoracic pressure changes.

During the course of the study, the investigators began to feel that they could pick out etiological types of heart disease, and roughly evaluate cardiac status, by study of the kymographic tracing. Partly to test this thesis, two groups of patients were studied—those in whom the clinical diagnosis was known prior to interpretation, and those in whom the diagnosis and fluoro-

TABLE I

Series 1—64 Cases
Diagnosis known prior to interpretation of electrokymogram

Classification of Kymograms	Cases	Per Cent	
Diagnostic	2	3.1	34.3
Compatible with diagnosis	20	31.2	
Equivocal	18	28.1	
Within normal limits[a]	24	37.5	

[a] 19 cases, or 29.7 per cent of the series, with serious heart disease had apparently normal kymograms.

Series 2—71 Cases
Diagnosis unknown prior to interpretation of electrokymogram
Series included normal cases at random

Classification of Kymograms	Cases	Per Cent	
Diagnostic	4	5.6	60.5
Compatible with diagnosis	39	54.9	
Equivocal	6	8.5	
Interpretation not in agreement with diagnosis	22	31.0	
A. Kymogram failed to pick up abnormalities	16	22.5	
B. False positive kymogram	6	8.5	

scopic findings were unknown prior to interpretation of the tracings. Table 1 summarizes the results. During this comparison, the criteria used in interpretation were constantly changed as more was learned, but the comparison remains largely valid.

COMMENT

It would appear that the primary application of the electrokymograph at the present time, in its present state of development, is as a physiological research tool. It is for the clinical investigator rather than for the clinician. With further improvement, further delineation of normal variations, and correlation with other cardiac cycle events, it may prove to be a valuable addition to the array of diagnostic aids available to the clinician. Future developments, such as the new fluoroscopic image intensifier recently announced, may be used in conjunction with the apparatus. Used in conjunction with ballistocardiography and cardiac catheterization, this device may extend the frontiers of our knowledge and, if a satisfactory method of wave amplitude standardization can be found, may prove to be a relatively simple method of determining cardiac output.

SUMMARY

1. A description of the electrokymograph and an evaluation of its status as a clinical tool has been presented.

2. It appears that this device, in its present form, is primarily an aid to the clinical investigator, rather than to the clinician. It may be of diagnostic value in a select group of patients when used with discretion.

ADDENDUM

Many of the ideas and some of the data presented in this paper are not those of the authors, but the opinions are their own. The authors wish to thank Drs. B. R. Boone, G. F. Ellinger, and E. F. Randak, for helpful advice and criticism. We are indebted to Mr. Willis E. Drummond, Jr., for technical assistance.

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PITUITARY MYXEDEMA: REPORT OF THREE CASES *

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In 1940 Means, Hertz and Lerman [1] described a group of patients with myxedema who did not respond well to thyroid treatment. When the usual doses of desiccated thyroid were given, the patients became weaker, and in some the picture of adrenal insufficiency developed. It was shown that in these patients myxedema was only part of a more widespread glandular failure resulting from primary insufficiency of the anterior pituitary gland. The name "pituitary myxedema" was suggested for this condition. Similar cases have been reported by other authors.[2-8]

Pituitary myxedema may be regarded as a special type of anterior pituitary failure or panhypopituitarism, in which the secondary thyroid failure dominates the clinical picture. The classical picture of anterior pituitary failure, long known as "Simmonds' disease," has undergone some revision recently. Sheehan [9] has clearly shown that progressive wasting is by no means an essential feature of the syndrome. Secondary failure of the thyroid, adrenal cortex, or gonads, may be present in varying degree. Thus the clinical picture may resemble that of hypothyroidism, Addison's disease, or gonadal deficiency, although features of all three are usually present. The use of the term "pituitary myxedema" to designate a special type of anterior pituitary failure may be criticized. However, the close resemblance of these patients to the picture of primary myxedema would appear to justify this special designation. This has been well discussed by Cluxton, Bennett, and Kepler.[6]

Three patients with anterior pituitary failure masquerading as myxedema have been observed in the McGuire Veterans Administration Hospital and will be described.

Case 1. G. W., a 36 year old white man, was admitted to the Veterans Administration Hospital February 26, 1947 with a chief complaint of weakness of three years' duration. He had been well until 1943 when, while in North Africa with the Navy, he began to notice intolerance to cold. This became worse, and when he was later stationed in England, cold weather was almost unbearable. At the same time he noticed weakness which progressed to the point that he had great difficulty in carrying out any assignment. He developed loss of libido and impotence. He began to notice puffiness about the eyes, and his fingers felt stiff and the skin thick. His eyebrows

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became thinner and axillary and pubic hair became sparse. He was twice hospitalized overseas, but returned to duty. He was discharged from the Navy in December 1945 on points. Since his discharge he had attempted manual labor, but had to give it up because of weakness and fatigability. He had not lost weight. His past history was non-contributory except for mumps with a left orchitis at the age of 20.

Examination revealed a well developed and nourished man, appearing younger than his stated age. The facies was phlegmatic, with puffiness about his eyes and face giving a leonine appearance. The skin was very pale, dry, coarse, and scaly, and showed fine wrinkling. The hands and fingers appeared thick and puffy. Hair on the head was coarse but of normal distribution. The eyebrows were thin. The beard was sparse. Axillary and pubic hair were almost absent. Blood pressure was 115 mm. Hg systolic and 80 mm. diastolic and pulse rate 80. The pupils and fundi were normal. The heart, lungs, and abdomen were normal. The genitalia were not remarkable except that the left testicle was small. Rectal examination was negative. There was no lymphadenopathy. Neurological examination was negative. Visual fields were normal.

Laboratory studies: Urinalysis negative. Red blood cells 3,890,000. Hemoglobin 11.9 gm. Hematocrit 36. White blood cells 6,900, with 50 per cent neutrophiles, 40 per cent lymphocytes, 5 per cent eosinophiles, and 5 per cent monocytes. Kahn negative. Basal metabolic rates were -27 per cent and -32 per cent. Serum cholesterol 262 mg. per cent. Total protein 7.8 gm., albumin 5.3 gm., and globulin 2.5 gm. Blood urea nitrogen 19 mg. per cent. Fasting blood sugars from 72 mg. per cent to 83 mg. per cent. Serum sodium 130 m.eq. per liter. Serum potassium 5 m.eq. per liter. Serum chloride 104 m.eq. per liter. CO_2 combining power 25 m.eq. per liter. Serum calcium 10.5 mg. per cent. Serum alkaline phosphatase 0.4 unit. Glucose tolerance test showed a flat curve with the following blood sugar values: Fasting 82 mg. per cent; one-half hour 83 mg. per cent; one hour 90 mg. per cent; two hours 96 mg. per cent; three hours 111 mg. per cent. Insulin tolerance test [10] (using 0.05 unit/kg.) showed increased insulin sensitivity but almost normal recovery from hypoglycemia, with blood sugar values as follow: Fasting 72 mg. per cent; 20 minutes after insulin 27 mg. per cent; 30 minutes 35 mg. per cent; 45 minutes 47 mg. per cent; one hour 60 mg. per cent; one and one-half hours 74 mg. per cent; two hours 64 mg. per cent; 45 minutes after adrenalin 90 mg. per cent; one hour after adrenalin 86 mg. per cent. Kepler water test [11] was positive, with "A" equal to 8. Circulation time from arm to tongue was 20 seconds. Electrocardiogram showed low voltage of QRS complexes and T waves, with a PR interval of 0.22 second. Chest roentgen-ray was negative, with a cardio-thoracic ratio of 40 per cent. Roentgenogram of the skull showed a markedly enlarged pituitary fossa measuring 22 by 15 mm., with erosion of the posterior clinoids and of the dorsum sellae. This was interpreted as indicative of an expanding intrasellar mass. Roentgen-rays of the hands and feet were negative.

Because of the occurrence together of hypothyroidism, diminished gonadal function, and laboratory evidence of impaired function of the adrenal cortex, it was felt that the patient had primary insufficiency of the anterior pituitary gland. The roentgen-ray appearance of the sella turcica strongly suggested a pituitary tumor. The most likely diagnosis was thought to be chromophobe adenoma. Because of the slowness of its growth and the absence of signs of pressure on the optic chiasm, surgical intervention was considered unwarranted. A course of irradiation of the pituitary totalling 2,100 R was given. At the same time, desiccated thyroid one-half grain daily was begun, and a daily supplement of 5 gm. of sodium chloride was added to the diet. Ferrous sulfate was also given for the anemia. During the next six weeks, the thyroid dosage was gradually increased to two grains daily. On this dosage, the patient felt much improved, the clinical signs of myxedema disappeared,

and the basal metabolic rate rose to between − 10 per cent and − 4 per cent. The serum cholesterol was somewhat lowered, averaging 232 mg. per cent. At no time during thyroid administration did any untoward symptoms occur.

One month after the beginning of thyroid therapy, intramuscular injections of testosterone propionate were begun. At first 25 mg. was given three times a week and later the dosage was increased to 50 mg. On this dosage, definite sexual stimulation was noted, and intercourse was possible for the first time in eight months. The patient's strength, feeling of well-being, and mental outlook improved remarkably. He was given frequent passes to return home. He was able to play tennis, and reported his sexual function as satisfactory. Increase in the beard and in the frequency of shaving was noted. On June 12, six tablets of uncombined testosterone, 75 mg. each, were implanted subcutaneously in the left subscapular area. On June 25, two more pellets were implanted on the right, making a total of eight, or 600 mg. Intramuscular injections of testosterone were discontinued. The patient was discharged on July 2, 1947, with instructions to continue taking thyroid two grains daily and two teaspoonfuls of extra salt daily, and to supplement the implanted testosterone if necessary with the use of sublinguets of methyl testosterone, 10 mg. each.

The patient has now been followed for more than two years. He has felt very well and has been working steadily at heavy manual labor. When the effect of his testosterone pellets wore off he used methyl testosterone sublinguets averaging about 20 mg. daily, and continued to have adequate sexual function. In December 1947 another 600 mg. of testosterone pellets was implanted. He returned to the hospital in June 1948 because of nausea and dizziness following sulfonamide taken for a sore throat. He reported that he had been feeling somewhat weak for about three months. Examination showed definite growth of a moderate amount of chest, axillary and pubic hair. Blood pressure was 100/60. All signs of myxedema had disappeared. Serum sodium and potassium were normal. 17-Ketosteroid excretion was 4.6 mg./24 hours.

His nausea and dizziness subsided promptly, and were apparently caused by the sulfonamide drug. However, because of the possibility of subclinical adrenocortical deficiency, intramuscular injections of desoxycorticosterone acetate 1 mg. daily were begun. Thyroid two grains and salt two teaspoonfuls daily were continued. Testosterone pellets totalling 450 mg. were implanted. Two weeks later the patient was feeling stronger, blood pressure was 120/80, and 17-ketosteroid excretion was 6.9 mg./24 hours. No signs of abnormal salt retention were seen. Two pellets of DOCA, 75 mg. each, were implanted. He has felt well and has continued to work since. In February 1949, 150 mg. of DOCA were again implanted, and he was instructed to take methyl testosterone sublinguets 25 mg. daily in lieu of further testosterone implants. Thyroid and supplementary salt are being continued.

Case 2. G. F., a 28 year old white man, was admitted to the Veterans Administration Hospital February 25, 1947 complaining of weakness, dizziness, palpitation, backache, and swelling of the hands and feet. He stated that he had felt well until 1941 when he began to notice puffiness about the eyes. Later, he noticed swelling of the hands and feet. In 1943, he began to notice loss of libido and decline of sexual potency. All body hair was progressively lost and shaving was reduced to once a week. He grew increasingly weak anu suffered from dizziness and palpitation. He was twice hospitalized. At one institution, a diagnosis of brain tumor was made, and at another he was diagnosed as having myxedema with polyglandular deficiencies. In 1946, a course of thyroid was given but had to be stopped because of marked increase in his weakness. During 1946, he had one episode of unconsciousness with a high fever, from which he recovered. He had become irritable and despondent and had made one suicide attempt. His weight had fallen from 155 pounds to 140 pounds during the past four years.

On examination, the patient presented an immature, expressionless facies. The face and hands were puffy. The skin was very pale, sallow, dry and scaly. There were fine wrinkles about the eyes and mouth out of keeping with his otherwise youthful appearance. The beard was scanty and there was almost complete absence of axillary and pubic hair. Blood pressure was 90/70 and the pulse rate 68. Pupils and fundi were normal. The heart, lungs, and abdomen showed no abnormalities. The genitalia appeared normal except for somewhat small testes and absence of pubic hair. Neurological examination was negative. Visual fields were reported as normal.

Laboratory studies: Urinalysis negative. Red blood cells 3,230,000. Hemoglobin 8.9 gm. Hematocrit 33. White blood cells 4,450, with 33 per cent neutrophiles, 62 per cent lymphocytes, and 5 per cent eosinophiles. Kahn negative. Fasting blood sugars from 57 mg. per cent to 78 mg. per cent. Total protein 7.3 gm. Blood urea nitrogen 28 mg. per cent. Serum chloride 99 m.eq. per liter. CO_2 combining power 24 m.eq. per liter. Serum calcium 9.7 mg. per cent. Serum phosphorus 4 mg. per cent. Serum alkaline phosphatase 2.5 units. Basal metabolic rates — 37 per cent and — 39 per cent. Serum cholesterol 185 mg. per cent. Glucose tolerance test gave the following blood sugar values: fasting 73 mg. per cent; one-half hour 125 mg. per cent; one hour 88 mg. per cent; two hours 68 mg. per cent; four hours 55 mg. per cent; five hours 58 mg. per cent; six hours 72 mg. per cent. Kepler water test was positive with "A" equal to 1. Circulation time from arm to tongue was 14 seconds. Electrocardiogram showed low voltage of all complexes with flattened T waves and a PR interval of 0.24 second. Chest roentgen-ray was negative, with a cardio-thoracic ratio of 41 per cent. Roentgenogram of the skull showed the sella turcica to be moderately enlarged, measuring 16 by 12 mm., but without evidence of erosion. Roentgen-ray of the hands showed no abnormality.

On March 19, the patient was given a pass to return home. No therapy had been begun. While at home, he became acutely ill with nausea, vomiting, abdominal cramps, diarrhea, and a high fever. He was brought back to the hospital on March 21, unconscious, with temperature 105.8° and blood pressure 60/28. The diagnosis of an Addisonian crisis was made. Large amounts of intravenous saline, glucose, and plasma were given, and adrenal cortical extract and desoxycorticosterone acetate were given intramuscularly. During the next few days, the patient made a satisfactory recovery, the temperature returning to normal, and the blood pressure rising to 90/55. Injections of DOCA were continued, the dosage being gradually reduced from 10 mg. daily to 2.5 mg. daily. A supplement of 6 gm. of extra salt daily was added to the diet.

On March 27, desiccated thyroid one-half grain daily was begun. This dosage was gradually increased during the next two months to three grains daily. On this dosage, the basal metabolic rate rose to — 9 per cent. All clinical evidence of myxedema disappeared.

During April, intramuscular injections of testosterone propionate 25 mg. three times a week were begun. The dosage was later increased to 50 mg. Increase in libido and sexual potency was noted, and there was a striking change in the patient's mental outlook. He became much more cheerful and coöperative.

The roentgen findings suggested but did not conclusively prove the presence of a pituitary tumor. A supra-sellar cyst was considered. The diagnosis of chromaphobe adenoma, however, seemed more likely. In the absence of visual disturbance, surgical exploration was thought inadvisable. Irradiation of the pituitary gland was given during April in a total dosage of 1,200 R.

By June, the patient appeared to be stabilized on the above dosage of thyroid, DOCA, and testosterone. Blood pressure remained at 100/60. The patient felt normally strong and was anxious to return to work. On June 16, three pellets of desoxycorticosterone acetate, 75 mg. each, were implanted subcutaneously in the left

subscapular region, and four pellets of uncombined testosterone, 75 mg. each, were implanted on the right. Intramuscular injections of DOCA and testosterone propionate were discontinued. The patient continued to take thyroid three grains daily and a supplement of two teaspoonfuls of salt daily. He continued to feel well and was discharged on July 11, 1947.

The patient has been subsequently followed closely for more than two years. New implants of DOCA 225 mg. were given in June 1947, February 1948, September 1948, and February 1949. Testosterone implants of 225 or 300 mg. were given in June 1947, February 1948, May 1948, September 1948, and February 1949. When the effect of the latter has waned, he has taken supplementary sublinguets of methyl testosterone 10 to 20 mg. daily. With some lapses he has taken desiccated thyroid three grains daily. A second course of irradiation of the pituitary totalling 1,840 R was given in January 1948. In March 1948 ankle edema developed and the daily ration of salt was reduced to one teaspoonful. In August 1948, six months after the last previous DOCA implant, he developed another Addisonian crisis. With treatment he recovered, and the interval between subsequent DOCA implants was shortened to five months. It is planned to increase the dose of DOCA on the next implant.

The improvement in his general state of health and mental outlook has been striking. Except for the crisis mentioned above he has worked steadily. His weight has increased in two years from 140 pounds to 162 pounds. He feels normally strong. Sexual function is normal. He has suffered from occasional bitemporal headaches. There has been return of a moderate amount of pubic hair, and of a little axillary hair. The beard is somewhat more abundant, but still sparse. The blood pressure has remained low, ranging from 90/60 to 110/70.

The anemia initially present has improved, hemoglobin now ranging from 12.5 to 13.8 gm. Basal metabolic rate has varied from -9 per cent to -34 per cent, the lower figures possibly representing lapses in thyroid medication. Although the initial serum cholesterol level was normal, subsequent values of 260 and 275 mg. per cent have been found. Blood urea nitrogen has returned to a normal level of 16 mg. per cent. Repeated estimations of serum sodium, potassium, chloride and CO_2 combining power have been normal. The Kepler test remains strongly positive, with "A" equal to 1. 17-ketosteroid excretion was unfortunately not done prior to treatment, but subsequent determinations are still low, averaging 1.7 mg./24 hours. Semen examination has shown complete aspermia.

Case 3. J. W., a 48 year old white man, was admitted to the Veterans Administration Hospital on May 5, 1948, complaining of weakness and joint pains. His early life and development had been normal, and he was in good health in 1942 when he entered the Army. In 1943 he was hospitalized for six weeks for bilateral pleurisy. Shortly after recovery from this illness he began to suffer from pain and stiffness in all joints and in his back, aggravated by damp weather. At about the same time he began to notice progressive weakness. He was again hospitalized and was given a medical discharge for arthritis. Joint pains and weakness continued, and he was able to do little work. In 1944 he noticed gradual falling out of axillary, pubic and body hair, and his beard became increasingly scanty until he had to shave only once a week. In 1945 his libido began to decline, and within a year he was entirely impotent. At the same time he began to notice intolerance to cold, lassitude, anorexia and some weight loss. Altogether he lost about 15 pounds in the next three years. He became constipated, and suffered from dizziness and headaches. He had been hospitalized elsewhere in 1945 for treatment of anemia.

On examination the patient appeared at least 10 years older than his actual age of 48. The skin appeared extremely pale and pasty. There was excessive fine wrinkling about the eyes and mouth. Hair on the scalp was normal, but the eyebrows

were thin, especially in the lateral half. The beard was almost entirely absent. No axillary or trunk hair was present. A scanty amount of pubic hair was present. Blood pressure was 80/60, and pulse rate 70. The eyes, ears, nose and throat showed no abnormality. The fundi and visual fields were normal. All teeth had been removed. No abnormalities were noted in the heart, lungs or abdomen. The genitalia appeared normal except that the testes felt somewhat soft. The prostate felt normal. The musculature showed generalized wasting. Dorsal kyphosis was present. Neurological examination was negative.

Laboratory studies: Urinalysis negative. Red blood cells 3,800,000. Hemoglobin 11.0 gm. Hematocrit 34. White blood cells 7,300 with 42 per cent neutrophiles, 53 per cent lymphocytes, 1 per cent monocytes, and 4 per cent eosinophiles. Kahn negative. Basal metabolic rate was — 26 per cent. Serum cholesterol 340 mg. per cent. Total protein 6.3 gm. Blood urea nitrogen 19 mg. per cent. Fasting blood sugar 90 mg. per cent. Serum chloride 101 m.eq. per liter. Serum calcium 11.1 mg. per cent. Serum phosphorus 5.5 mg. per cent. Serum alkaline phosphatase 5 units. Glucose tolerance test showed a moderately flat curve with the following blood sugar values: fasting 90 mg. per cent, one-half hour 106 mg. per cent; one hour 101 mg. per cent; two hours 112 mg. per cent; three hours 106 mg. per cent; four hours 86 mg. per cent; five hours 90 mg. per cent. Insulin tolerance test (0.05 unit/kg.) showed increased sensitivity to insulin and some hypoglycemia-unresponsiveness with the following blood sugar values: fasting 73 mg. per cent; 20 minutes after insulin 30 mg. per cent; 30 minutes 30 mg. per cent; 45 minutes 42 mg. per cent; one hour 39 mg. per cent; one and one-half hours 51 mg. per cent; two hours 60 mg. per cent; 45 minutes after adrenalin 116 mg. per cent; one hour after adrenalin 116. mg. per cent. 17-Ketosteroid excretion was 1.6 mg. in 24 hours. Kepler water test gave a positive result with the quotient "A" equal to 6. Electrocardiogram showed low voltages in all complexes and PR interval of 0.20 second. Chest roentgenogram was negative except for a calcified nodule in the left apex. The heart was small with a cardio-thoracic ratio of 38 per cent. Roentgen-rays of the vertebrae, hands and knees showed some osteoporosis and slight narrowing of joint spaces. Skull roentgenogram showed a very large sella turcica, measuring 20 by 17 mm., with erosion of the floor. The anterior clinoids were normal, but only a faint shadow of the dorsum sellae was seen and the posterior clinoids could not be seen at all. These findings were interpreted as indicative of an intra-sellar tumor.

The patient was thought to have a chromophobe adenoma of the pituitary, causing anterior pituitary insufficiency, with secondary failure of thyroid, gonadal and adreno-cortical function. On May 20, 1948 substitution therapy was begun with desiccated thyroid one-half grain daily, testosterone propionate 25 mg. intramuscularly three times a week, desoxycorticosterone acetate 2.5 mg. intramuscularly daily, and salt three teaspoonfuls daily added to the diet. It soon became apparent that this amount of DOCA and salt was excessive. Although the blood pressure rose only to 100/70, nocturnal dyspnea developed after three days of treatment and moist râles were heard in the lung bases. A roentgenogram showed increase in heart size with cardio-thoracic ratio of 43 per cent. DOCA and salt were temporarily discontinued with relief of these symptoms. Subsequently DOCA 1 mg. daily and salt one teaspoonful daily were given without further dyspnea. The thyroid dosage was gradually increased to two grains daily. On this dosage the basal metabolic rate rose to — 6 per cent and the serum cholesterol fell to 200 mg. per cent. Excessive sexual stimulation was noticed with testosterone three times a week, and the injections were reduced to 25 mg. twice a week.

Irradiation of the pituitary was given from May 20 through June 12, a total of 1,585 R being given. Iron was given for the anemia but no improvement in the blood counts was seen. Subsequently two transfusions were given.

On the above program of glandular substitution therapy the patient gradually gained strength, but improvement was not as striking as with the two previous patients. He continued to complain of joint pains. It was decided to proceed cautiously with pellet implantations. On August 5, 150 mg. of desoxycorticosterone acetate and 300 mg. of testosterone were implanted, intramuscular injections of these substances being stopped. He was discharged on August 6, 1948 to continue taking thyroid two grains and salt one teaspoonful daily.

At home the patient noted normal sexual function for the first time in two years. His strength was somewhat improved but he still felt weak. His back and joints continued to be painful in damp weather. He did not gain weight. He did notice relief of his former dizziness.

He was readmitted for check-up on October 11, 1948. He appeared stronger, and reported that he was now shaving three times a week. Growth of some axillary and mammary hair was evident. Blood pressure was 110/70. The heart was not enlarged. One observer noted a sharply localized apical presystolic murmur. The lungs were clear. Hemoglobin had risen to 13.3 gm. Basal metabolic rate was −9 per cent. 17-Ketosteroid excretion was 1.9 mg. in 24 hours. It was thought that further DOCA might improve his weakness, and an additional 150 mg. was implanted on October 21. He was instructed to take sublinguets of methyl testosterone when the effect of his testosterone pellets wore off, and to continue taking thyroid two grains and salt one teaspoonful daily. He was discharged, to return in two months.

The patient did not return to the hospital until April 20, 1949. He had noticed exertion dyspnea on his return home and had discontinued all medication one month after leaving the hospital. He had taken no methyl testosterone, but stated that sexual function had remained adequate until January, when he again became impotent. He had attempted some work during the winter but gave it up because of weakness and painful joints. There had been no return of dizziness. His appearance on this admission was essentially as when he was first seen, except for the growth of some axillary, mammary, and pubic hair. Blood pressure was 105/70. Pulse rate was 80. The heart was not enlarged, but a definite rough mitral presystolic murmur was heard, which was considered typical of mitral stenosis. Fluoroscopy of the heart showed displacement of the esophagus by an enlarged left auricle. Electrocardiogram was within normal limits. Arm to tongue circulation time was 15 seconds.

Other laboratory studies were as follows: Hemoglobin 12.5 gm., red blood cells 4,400,000. Basal metabolic rate −29 per cent. Serum cholesterol 340 mg. per cent. Serum sodium 142 m.eq. per liter. Serum potassium 5.0 m.eq. per liter. Serum chloride 109 m.eq. per liter. CO_2 combining power 23 m.eq. per liter. 17-Ketosteroid excretion 2.6 mg./24 hours. Roentgen-ray of the sella turcica showed no change from previous films. Roentgenograms of the vertebrae, hands, and knees again showed slight osteoporosis and narrowing of joint spaces.

The presence of mitral stenosis seemed to explain the poor tolerance of the patient to DOCA and extra salt. It was decided to give no more of either. Desiccated thyroid two grains daily and intramuscular testosterone propionate 25 mg. twice weekly were resumed. Because the patient still complained of some exertion dyspnea, he was digitalized and maintained on digitoxin 0.2 mg. daily. He stated that his dyspnea was improved after this. A second course of irradiation of the pituitary gland totalling 3000 R was given. On June 1, 600 mg. of testosterone was implanted. The patient was allowed to return home, to continue taking thyroid and digitoxin. He returned for check-up six weeks later. He stated that he felt very much stronger, that sexual function was normal, and that he was now shaving every other day. He was still dyspneic on attempting strenuous exertion but showed no signs of congestive failure. He still complained of joint pains. Examination showed considerable improvement in his strength and appearance. The beard, axillary and pubic hair had increased markedly, and now appeared almost normal.

Discussion

I. Clinical Features: These patients all presented histories and physical findings fairly typical of myxedema. Subsequent studies showed each to be an instance of primary pituitary failure with secondary hypothyroidism together with secondary hypogonadism and deficiency of the adrenal cortex.

In the histories obtained the outstanding feature distinguishing these cases from ordinary myxedema is the loss of genital function. Loss of libido, impotence, and complete loss of pubic and axillary hair are indicative of a specific loss of gonadal function. Genital function may be decreased in primary myxedema but is seldom totally lost.[12]

The symptoms of adrenal cortical deficiency are more difficult to recognize and may be entirely latent. Extreme weakness and inability to work was a major complaint of each of these patients. Two of the patients had lost some weight but showed no marked wasting. One patient had several spontaneous Addisonian crises, but we believe this is unusual. Special laboratory tests are usually necessary to demonstrate the adrenocortical deficiency. None of these patients showed any pigmentation of the type seen in Addison's disease. This has been commented on by others.[7]

On physical examination, the typical facies and other physical findings of myxedema were present. The following special features may be indicative of the primary pituitary failure. The beard was extremely scanty, and axillary, pubic, and body hair were almost totally absent. The skin showed excessive fine wrinkling, especially about the eyes and mouth. This may produce an aged appearance, as was noted in the third case. On the other hand, the first two patients, who were younger, appeared immature and youthful in spite of some wrinkling. This may be due to the absence of the beard and to a lack of some testosterone effect in the skin. The testes were somewhat small or soft in each case.

All three patients showed anemia which resisted efforts at correction until adequate hormonal substitution was achieved. Then the hemoglobin tended to remain normal without further anti-anemic therapy.

Differential blood counts on these patients showed a constant slight lymphocytosis and an increase in eosinophiles which may be related to decreased adreno-cortical activity.

The lowered basal metabolic rate was accompanied by an elevated serum cholesterol in two patients. In the third the serum cholesterol was initially normal but later became elevated after a lapse in thyroid administration. The return of the basal metabolic rate and serum cholesterol towards normal on thyroid treatment seemed quite similar to that expected in primary myxedema.

The Kepler water diuresis test was strongly positive in all three patients and offered presumptive evidence of adreno-cortical deficiency. Serum electrolyte studies showed no significant abnormalities.

The combined use of the insulin tolerance test and the determination of

17-ketosteroid excretion has been suggested as the most definitive index of anterior pituitary failure.[5] The insulin tolerance test showed normal hypoglycemia-responsiveness in the first patient, and only partial hypoglycemia-unresponsiveness with the third. It was not carried out on the second patient, who showed some fasting hypoglycemia and other evidence of severe adreno-cortical deficiency. 17-Ketosteroid excretion prior to any treatment was measured on only the third patient. The value of 1.6 mg./24 hours is low, but is not in the 0 to 0.5 mg. per cent range considered indicative of anterior pituitary failure.[6] It is suggested that these two tests, while extremely useful, may not detect instances of partial anterior pituitary failure. On clinical grounds there is reason to believe that our first patient had only mild adreno-cortical deficiency, whereas the second patient had frank symptoms of Addison's disease. It is likely that, as the pituitary gland is progressively damaged, the most vital function of maintaining stimulation of the adrenal cortex is preserved as long as possible, at the expense of gonadotropic and thyrotropic function. Thus patients with pituitary damage may show pronounced hypogonadism and hypothyroidism with relatively little evidence of adreno-cortical failure. Tests which measure secondary glandular failure may vary accordingly.

Roentgenographic evidence of a pituitary tumor is almost incontrovertible evidence of the primary status of pituitary failure in cases such as these. This finding was definite in the first and third cases and was strongly suggested in the second. Many other types of pituitary damage produce no such visible sellar changes, and the diagnosis must be made from other data.

II. Treatment: The primary lesion in each of these cases appeared to be a chromophobe adenoma of the pituitary. Any attempt at surgical removal of the tumor seemed likely to destroy whatever remaining pituitary tissue there might be, and was considered unwarranted. The tumor was irradiated in each case in the hope of slowing its growth. It is impossible to evaluate the effect of irradiation since hormonal substitution therapy was instituted simultaneously.

At the present time there is no pituitary extract of practical value for maintenance replacement therapy. Treatment of necessity consists of substitution for the various secondary glandular deficiencies that are present. This can be accomplished with considerable success, as at least two of these patients illustrate.

Means, Hertz and Lerman,[1] and others [2-4] have stressed the danger of treatment with thyroid alone. Our second patient had been given thyroid previously with an alarming aggravation of his weakness. After he received adequate substitution therapy for his adrenal cortical failure, full dosage of thyroid was well tolerated. With adequate thyroid administration, all findings of myxedema were relieved in each case.

The administration of testosterone appeared to play a paramount rôle in improving the strength, sense of well being, and psychological outlook of

these patients, in addition to restoring sexual function and secondary sexual characteristics. The subcutaneous implantation of testosterone pellets appeared to be the most satisfactory method of administration. Sublingual methyl testosterone was used at times, but no real evaluation of its effectiveness could be made. One patient stated that he obtained more effect from the implants. The pellet implantation was preferred because it eliminated the uncertainty of whether the patient was actually taking the prescribed dosage.

The use of desoxycorticosterone and supplementary salt intake is important where deficiency of the salt retaining adreno-cortical steroids is present. It has undoubtedly been life saving in our second patient. However, it must be used with caution as our third patient illustrates. Overdosage of salt and DOCA caused prompt development of symptoms of cardiac failure. The subsequent discovery of a previously unrecognized murmur of mitral stenosis led to some speculation as to whether excessive salt and DOCA might have produced myocardial and valvular damage, similar to that demonstrated by Selye in the rat.[13] Review of roentgen-rays and electrocardiograms showed no significant changes after DOCA to support this possibility. It is much more reasonable to assume that the patient had had an old mitral stenosis which was unrecognized until after symptoms of congestive failure developed. Even without such a complicating factor the use of DOCA and salt may be dangerous. The need for salt retaining hormone replacement should be carefully evaluated. A supplement of salt added to the diet may be all that is needed. If indicated, DOCA should be given intramuscularly over a prolonged period, with careful observation for rises in blood pressure and for signs of excessive salt retention. When the proper dosage has been determined DOCA pellets can be implanted subcutaneously with quite satisfactory results.

The over all result of treatment is considered quite gratifying in the first two patients. Both have returned to steady work after prolonged periods of disability. Both are living normal married lives and regard themselves as well. In the third case the course has been less satisfactory. The patient is considerably stronger and has normal sexual function, but he still feels under par and suffers from exertion dyspnea and joint pains. The complicating cardiac lesion may be blamed for the dyspnea, and the joint pains are probably unrelated to his glandular deficiencies. However, it is possible that treatment with other adrenal steroids might improve his status. A cautious trial with hog lipo-adrenal extract is contemplated.

We believe that by the judicious combination of thyroid, adrenal cortical and gonadal substitution products, patients such as these can be successfully managed. The degree of deficiency of each gland will vary in different patients, and the amount of substitution necessary for each gland must be gauged accordingly. Proper dosages can be arrived at only by a prolonged period of trial.

Conclusions

1. Three cases of primary anterior pituitary insufficiency masquerading as myxedema have been presented.

2. The diagnostic features of these cases have been discussed.

3. It is believed that these cases can be successfully managed by the judicious combination of thyroid, adrenal cortical, and gonadal replacement therapy.

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THE SERUM PROTEINS IN RHEUMATOID ARTHRITIS *

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One of the unexplained aspects of rheumatoid (atrophic) arthritis is its effect on the proteins of the blood. Using sulfate fractionation, Davis [1] found that severe rheumatoid arthritis is regularly accompanied by a decrease in the plasma albumin and an increase in the plasma globulin, particularly the euglobulin fraction. The albumin-globulin (A–G) ratio was correspondingly lowered, as follows:

normal range	1.81–2.35 (average 2.12)
rheumatoid arthritis:	
severe	0.69–1.07 (average 0.90)
moderate	1.11–1.83 (average 1.47)
"arrested"	1.24–1.95 (average 1.52)

Significant changes were not found in the total protein. A similar trend was observed by Scull, Bach and Pemberton,[2] using serum.

Subsequently, several groups of observers examined the blood in this disease by the more sensitive technic of electrophoresis.

The principal advantage of electrophoresis, as described by Tiselius [3] and others, is that it measures protein components with far greater accuracy than do chemical procedures; the principal disadvantages, that it is a tedious and exacting technic, and that it fails to distinguish between components which have approximately the same mobility. Under suitable circumstances, serum protein molecules migrate in the presence of an electric current, the different protein components moving with different speeds. The advancing border or boundary of each component has a concentration of protein molecules which give it a refractive index differing from that of the surrounding medium. Consequently a beam of light will be deflected at this point, the degree of deflection depending on the concentration of the protein. With the aid of a complex optical apparatus, the deflection occasioned by each component of protein can be photographed as a peak. The distances between peaks are thus a measure of the relative velocities of the various components and the area beneath each peak is proportional to the size of the component which produced it. The chamber usually employed is in the form of a U and the patterns are referred to as descending or ascending depending on the arm of the U from which they are obtained.

In order of decreasing mobility, the components of human serum are: albumin, alpha globulin (increased by inflammation or tissue destruction), beta globulin (concerned in the transport of lipids), and gamma globulin

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(antibodies). Depending on technical details, any of these components may appear as a double peak, e.g. alpha$_1$ and alpha$_2$. It should be emphasized that any one peak may represent a number of different proteins, which are classified together by this method because they happen to have identical or nearly identical mobilities.

The designation T was applied by van der Scheer and Wyckoff [4] to a component intermediate between the β and γ globulins, appearing in the sera of horses immunized with the toxins of tetanus or diphtheria, but lacking in the sera of horses immunized with pneumococci.[5] Although the size of the T component varies directly with the strength of the antitoxin, it has not been determined whether T consists solely of antibodies or represents chiefly a more or less non-specific side-effect of immunization with some antigens in some species.[6] The T component is apparently identical with the fraction of human serum which has been designated γ_1 by Deutsch, Alberty and Gosting.[7] Present in small amount in "normal" human serum, this component carries some of the antibodies. In the terminology of Deutsch et al., the classical γ globulin becomes γ_2.

Electrophoretic data on the blood in rheumatoid arthritis given in several papers quoted from the Scandinavian literature by Dole and Rothbard [8] may be summarized as follows:

albumin: decreased
α globulin: slight to moderate increase
β globulin: little change
γ globulin: slight to marked increase

The range of alteration in the α and γ globulins is attributable in part to varying stages of clinical disease and perhaps also in part to the inclusion of cases in which the diagnosis of classical rheumatoid arthritis was questionable. Malmros and Blix [9] examined sera from seven patients with diagnoses of rheumatoid arthritis. Their two subjects who failed to show an increase in γ globulin had A–G ratios by a salting-out method of 2.2 and 2.0 respectively. These patients were presumably in a quiescent phase of the disease. Dole and Rothbard [8] made 10 electrophoretic examinations of the serum of a patient with typical rheumatoid arthritis, between the seventy-sixth and two hundred eighty-sixth days of his disease. In addition to depression of albumin and A–G ratio, they found both α fractions elevated to more than twice normal values during the early stages, later falling to approximately normal levels, β globulin at or near the lower limit of normal throughout, and γ globulin with fair consistency about 35 per cent above normal. In an electrophoretic study of the blood of 23 patients with rheumatoid arthritis, Perlmann and Kaufman [10] found an increase in α globulin early in the disease and increased γ globulin later in its course.

In order to avoid uncertainties inherent in some of these reports, we have used routine serum protein determinations for a preliminary screening of

patients with typical rheumatoid arthritis. This permitted the selection of sera with low A–G ratios for further study by more sensitive procedures.

Materials and Methods

Subjects. In the selection of patients, those in whom there might be any question of the diagnosis of classical rheumatoid arthritis were excluded. The minimal requirements were a fairly symmetrical involvement of the proximal interphalangeal finger joints and a disease duration of one year. The degree of activity of the disease process was estimated on the basis of local heat, swelling, tenderness and pain and, when available, a recent erythrocyte sedimentation rate.

Measurement of Serum Proteins by Chemical Means. These determinations were performed by Miss Hester Snider, through the courtesy of Dr. John G. Reinhold. The procedure used was the biuret method of Kingsley.[11]

Electrophoresis. Dr. Florence B. Seibert of the Phipps Institute, Philadelphia, and Dr. T. L. McMeekin of the Eastern Regional Research Laboratory of the U. S. Department of Agriculture each kindly consented to examine two sera by this method. Dr. Seibert used a veronal buffer at pH 8.5–8.6, ionic strength 0.1, time two hours. Dr. McMeekin used a veronal buffer at pH 8.28, ionic strength 0.1, time three and one half hours.

Determination of Gamma Globulin by an Immunologic Method. This was done by Dr. Bacon F. Chow of the Squibb Institute for Medical Research, New Brunswick, N. J. The method used is based on the antigenic individuality of serum protein fractions. Previously described [12] for the determination of human serum albumin, it has been subsequently applied to other protein fractions.[13] Rabbits are immunized with purified fractions of human serum protein, care being taken not to over-immunize, in order to avoid cross-reactions. The precipitate which forms when the rabbit antiserum is added in optimal quantity to the human serum being tested is measured in a photoelectric turbidometer and the results are translated into actual values by comparison with known standards.

Results

Values for serum proteins obtained with the biuret method of Kingsley [11] are presented in table 1, arranged in order of decreasing A–G ratio. These results are in agreement with previous observations [1, 2] that this ratio is lowered in active severe rheumatoid arthritis. None of these patients had complications which might be expected to influence serum proteins, with the possible exception of number 18. This patient had undergone a supracondylar amputation two months previously, for an intractable infection of the foot. At the time of examination his stump was still draining very slightly. Among complications presumably related to the arthritis were severe iritis in number 30 and moderate pitting edema of the ankles in number 26. Characteristic subcutaneous nodules were present over the

TABLE I

Serum Proteins in Patients with Rheumatoid Arthritis (Chemical Method)

Patient No.	Sex and Color	Age yr.	Duration of Dis. yr.	TP Gm.	Alb. Gm.	Glob. Gm.	A/G	Activity of Disease	Extent of Disease	Physical Activity	Degree of Apparently Permanent Crippling
1 Cos	F W	65	20	6.8	4.9	1.9	2.5	inactive	widespread	bedfast-necessity	total
2 Hag	F W	44	21	7.0	4.9	2.1	2.3	inactive	chiefly hands	ambulatory	nil
3 Pol	F W	51	6	6.3	4.3	2.0	2.1	inactive	moderate	ambulatory	nil
4 Sch	M W	36	1	6.4	4.6	2.2	2.1	slight	chiefly hands	ambulatory	nil
5 Sow	M W	60	7	7.3	4.8	2.5	1.9	slight	moderate	ambulatory	slight
6 Aur	F W	23	1	7.0	4.6	2.4	1.9	slight	moderate	ambulatory	nil
7 Poo	M W	55	10	6.3	4.1	2.2	1.8	slight	widespread	ambulatory	slight
8 Har	F W	44	3	7.0	4.5	2.5	1.8	inactive	chiefly hands	ambulatory	nil
9 Row	F W	70	1	7.5	4.7	2.8	1.7	slight	moderate	ambulatory	nil
10 Szk	F W	45	3	6.8	4.3	2.5	1.7	slight	slight	ambulatory	nil
11 Cla	M W	44	6	6.6	4.1	2.5	1.6	slight	widespread	ambulatory	slight
12 Idd	M W	18	2	7.4	4.5	2.9	1.5	moderate	widespread	bedfast-choice	moderate
13 Win	F W	47	6	7.6	4.6	3.0	1.5	questionable	hands	ambulatory	slight
14 Wil	F W	47	1	5.3	3.1	2.2	1.4	moderate	widespread	bedfast-choice	nil
15 Fry	M W	62	14	6.7	3.9	2.8	1.4	slight	widespread	ambulatory	slight
16 Hos	F W	20	3	6.4	3.7	2.7	1.4	slight	widespread	chair 3 yr.	moderate
17 Lap	M W	23	3	8.1	4.8	3.3	1.4	moderate	widespread	ambulatory	slight
18 Mey	M W	59	12	6.1	3.5	2.6	1.3	moderate	widespread	bedfast-necessity	moderate
19 Kra	F W	50	4	6.8	3.6	3.2	1.3	moderate	moderate	ambulatory	slight
20 Hav	M W	58	27	6.8	3.7	3.1	1.2	slight	widespread	bedfast-necessity	total
21 Lud	M W	46	1	7.5	3.9	3.6	1.1	moderate	widespread	ambulatory	slight
22 Eva	M W	42	9	7.8	4.1	3.7	1.1	slight	widespread	ambulatory	slight
23 Pen	F W	59	6	8.1	4.1	4.0	1.0	slight	widespread	up in walker	moderate
24 Rod	M W	54	6	7.1	3.5	3.6	1.0	slight	widespread	ambulatory	moderate
25 She	M W	51	1	7.6	3.6	4.0	0.9	slight	widespread	ambulatory	slight
26 Fle	M W	62	1	5.0	2.4	2.6	0.9	moderate	moderate	bedfast-choice	slight
27 Boo	M C	51	6	7.7	3.8	3.9	0.9	moderate	widespread	ambulatory	slight
28 Mau	M W	38	1	5.7	2.5	3.2	0.8	marked	widespread	bedfast-choice	slight
29 Kne	F W	58	13	7.1	2.9	4.2	0.7	moderate	widespread	bedfast-choice	slight
30 Pom	M W	33	13	7.9	3.1	4.8	0.6	marked	widespread	chair	severe

Total protein (TP), albumin (Alb.) and globulin (Glob.) are expressed in grams per 100 c.c.

upper ulna in numbers 7, 11, 18, 26 and 30. Despite the difficulty of measuring the finer gradations in the activity of the disease, it is evident that a relation exists between this factor (taken in conjunction with the extent of the disease) and the A–G ratio.

Sera from two of these patients, numbers 21 and 22, were submitted to Dr. Seibert and from two others, numbers 25 and 27, to Dr. McMeekin for electrophoretic analysis. The results are presented in table 2. Calculations were made from descending patterns by the same method in all cases.

TABLE II

Serum Proteins in Patients with Rheumatoid Arthritis (Electrophoresis)

Patient	Alb. %	Globulin					A/G
		$\frac{\alpha_1}{\%}$	$\frac{\alpha_2}{\%}$	$\frac{\beta}{\%}$	$\frac{T(\gamma_1)}{\%}$	$\frac{\gamma(\gamma_2)}{\%}$	
No. 21	34.8	8.6	17.1	19.0	—	20.5	0.53
No. 22	39.1	6.6	12.9	15.7	4.9	20.9	0.64
No. 25	33.8	5.4	11.5	14.9	8.9	25.5	0.51
No. 27	37.1	4.0	13.0	13.0	5.7	27.4	0.59
Normal (average)*	53.3	8.0	10.4	13.8	—	14.2	1.15

* Data of Dr. Seibert.
The protein components are expressed in per cent of total area.

Through the courtesy of Dr. Seibert, normal values are included for comparison. The A–G ratio of any serum, whether normal or pathological, is lower by electrophoresis than by chemical methods because of differences in separation inherent in the methods. A tracing from the pattern of number *22* appears in figure 1, together with a normal for comparison.

The results shown in table *2* are in general agreement with those which have been recorded by other observers, the principal globulin increments occurring in the α_2 and γ (γ_2) components. The presence of a T or γ_1 component in the serum of rheumatoid arthritis has not been reported by previous observers, presumably because of differences in the technic of electrophoresis. As already stated, this fraction is attributable to immunization, but whether it represents actual antibodies or merely a side-effect is unknown.

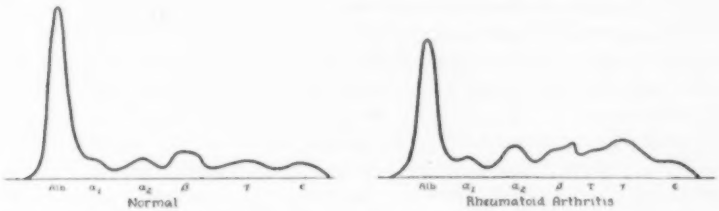

FIG. 1. Tracings of descending electrophoretic patterns of representative sera. The arthritis serum is that of patient number *22* in tables 1 and *2*. The reason for the β disturbance in this record is not completely understood. Similar β disturbances occur in other pathological sera. ϵ is a conductivity effect which is disregarded in calculating protein areas. These patterns were made available through the kindness of Dr. Florence Seibert.

Sera from 10 other patients in table 1, numbers 14, 16, 17, 18, 19, 20, 23, 24, 26 and 29, were submitted to Dr. Chow for estimation of γ globulin by his immunologic method. He found this component abnormally high in all, the values with one exception (number 16) being more than twice the normal. Two samples, numbers 24 and 29, contained over 25 per cent γ globulin.

DISCUSSION

It is known that inflammation or tissue destruction is accompanied by an increase in serum α globulin.[14] The reason for this association is suggested by the observations of Menkin,[15] who has shown that chemical injury to the protoplasm of cells can cause the liberation of a variety of abnormal substances derived from the breakdown of normal cellular proteins. Several of these substances are recognizable by their specific physiologic activity. Some (leukotaxine, which attracts leukocytes, and necrosin, which is a tissue irritant) remain at the site of injury, while others, including those capable of causing leukocytosis, leukopenia or fever, enter the circulation. Menkin [15] has found that one of the latter, the leukocytosis-promoting factor, when examined electrophoretically, moves with α_2 globulins of exudates.

This particular agent was probably not responsible for the α globulin rise reported by Dole and Rothbard [8] since their patient, like most rheumatoid arthritics, did not have much leukocytosis (or fever), but the implication regarding the relation of inflammation to elevated serum α globulin is obvious. These considerations also help to explain the relation between the erythrocyte sedimentation rate and inflammation or tissue destruction, as it has been shown [9, 16] that the sedimentation rate usually varies directly with the serum α globulin.

The γ globulin is responsible for the major portion of the globulin increment in rheumatoid arthritis. This is the fraction in which antibodies are characteristically found. Although it is debatable (cf. Boyd [17]) whether the γ component consists solely of antibodies, there is general agreement that an increase in this fraction usually signifies increased antibody production.

In the absence of a serologic test which is specific for rheumatoid arthritis,[18] the existence of antibodies aroused by this disease can only be inferred. However, support for the concept that antibodies are present in excess in the sera of patients with active severe rheumatoid arthritis has come from an unexpected quarter. Evidence to be presented elsewhere [19] indicates that "hyper-immune" states are apt to be accompanied by impairment of the systolic blood pressure rise in response to the intravenous injection of epinephrine, and that, by this criterion, patients with rheumatoid arthritis have excessive numbers of antibodies in proportion to the activity and extent of their disease process and also in proportion to the degree of lowering of their A–G ratios.

Identification of the origin and nature of the antigen which is responsible for the presumed antibodies of rheumatoid arthritis lies in the future. The antigen is not necessarily derived from an invading microörganism but could be produced from the body's own tissues. Whatever its source, the strength of the immune response indicates that the patient is undergoing prolonged and intensive immunization.

Union of antigen and antibody is doubtless responsible for the joint lesions of serum sickness and probably for those of acute rheumatic fever. It is perhaps also the cause of the cardiac lesions of rheumatic fever and, according to a recent suggestion,[20] the cause of the rheumatic-type heart damage which is often found on postmortem examination of severe rheumatoid arthritis, where it not infrequently appears to have been the principal cause of death. But it does not seem reasonable to apply this explanation to the joint lesions of rheumatoid arthritis in view of the long duration of their active stage as compared with the transient nature of the synovitis of serum sickness and acute rheumatic fever. Instead, we incline to the view that the same disturbance which produces an antigen in rheumatoid arthritis also causes a partial breakdown of cellular protoplasm into an irritant substance analogous to Menkin's [21] necrosin. The apparent failure of the patient's antibodies to neutralize this irritant implies that it is not antigenic, i.e., does not arouse antibodies. In this respect it would be like the other protein

breakdown products mentioned above. Their non-antigenicity, which is probably of vital importance,* may be explained by assuming that they do not differ sufficiently from native proteins to be recognized as foreign by the antibody-producing apparatus of the host.

It is known that intensive immunization of the horse [22] or the rabbit [23] causes a secondary hypoalbuminemia. Malmros and Blix [9] have suggested that this effect may be produced in either or both of two ways: (a) through the action of a theoretical regulatory mechanism governing the osmotic pressure levels of blood colloids or (b) on the better established principle of competition between albumin and the various globulins for available raw materials. The evidence of Zeldis et al.[24] indicates that in this respect plasma globulin has a higher priority than plasma albumin. In view of the importance of albumin in tissue nutrition, it therefore appears that the patient with severe rheumatoid arthritis is depleting his plasma albumin and hence his general nutrition as the price of excessive antibody production. Furthermore, Whipple and Madden [25] point out that the globin component of hemoglobin is interchangeable, after modification, with plasma proteins. In reviewing the evidence for a dynamic equilibrium between plasma proteins and cell proteins, they regard protein reserves in the tissues as capable of being mobilized and modified within the cell and contributed on demand to the blood stream. From this standpoint, the severe rheumatoid arthritic is paying for a prolonged high level of antibody production not only with plasma albumin and general tissue nutrition but also with hemoglobin.†

Thus the tragedy of rheumatoid arthritis has overtones of irony. Apparently the patient is sacrificing his hemoglobin and the nutrition of his tissues for the sake of making an excess of antibodies which not only do him no good, but may actually set the stage for a fatal heart disease, while the hypothetical irritant which is directly responsible for his pain and disability is too closely related to his own tissues to be capable of arousing serologic opposition.

Summary

In order to provide an explanation of the tendency of severe typical rheumatoid arthritis to depress the serum albumin-globulin ratio, sera selected for their low ratios on the basis of chemical fractionation were subjected to more sensitive procedures. Electrophoretic analysis of samples from four patients confirmed previous observations of increases in the α (inflammatory response) and γ (antibody response) components, chiefly the latter. In addition, three of the four showed a T component, not previously reported in rheumatoid arthritis serum. Less conspicuous in normal sera by the technic used herein, this fraction, like the γ component, is attributable to immuniza-

* For example, an animal which produced antibodies against its own leukocytosis-promoting factor would have difficulty surviving a pyogenic infection.

† While this appears to be an important contributory factor, it is not the sole mechanism in the production of anemia in rheumatoid arthritis. Cartwright et al.[26, 27] have presented evidence that chronic inflammation is accompanied by an obscure fault in the metabolism of iron which interferes with the production of hemoglobin.

tion. Examination of samples from 10 patients by an immunologic method, utilizing rabbit anti-human γ globulin serum, showed greatly increased γ globulin values, which averaged more than twice the normal content of this component.

In a discussion of the "hyper-immunity" of severe rheumatoid arthritis it is suggested (a) that the responsible antigen is not necessarily of infectious origin but could be derived from the patient's own tissues, (b) that the antibodies serve no evident useful purpose and (c) that for the sake of excessive antibody production the patient is apparently sacrificing his plasma albumin, his hemoglobin and his general tissue nutrition.

Conclusion

These data are interpreted as indicating that the hyperglobulinemia of active rheumatoid (atrophic) arthritis is the result of the combined effects of inflammation, tissue destruction and immunization, the last being the major contributor in all but the early stages of the disease.

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STUDIES IN DISORDERS OF MUSCLE. I. THE PROBLEM OF PROGRESSIVE MUSCULAR DYSTROPHY *

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Because of special circumstances present in Utah a study has been initiated which has as its object the investigation of diseases of muscle, especially progressive muscular dystrophy. Dr. Samuel C. Baldwin, an orthopedist recently deceased at the age of 90, initiated the local interest in this disorder. Dr. Baldwin himself studied a number of patients and with Dr. Fayette E. Stephens made valuable observations concerning the inheritance of this condition. The total incidence of dystrophy and other diseases of muscle in the area is unknown but there are many cases of muscular dystrophy in the local population. No data are available whereby one might compare the local incidence of these particular disorders with that in other areas.

The intermountain area presents an unique opportunity for the study of human inheritance. Although the total population is not great, it is unusual in that the family groups are, in general, large. In the early days of the area, which is only 100 years old in terms of a stable Caucasian population, many polygamous marriages occurred which extended further the number of descendants of a given individual. Because the population is relatively stable a high proportion is available for study. Furthermore, the Church of Jesus Christ of Latter-day Saints has fostered the keeping of detailed genealogical records from which accurate and complete pedigrees can be constructed.

The present paper is intended to serve as a brief background for subsequent reports and will include the presentation of a working classification of the muscular dystrophies as well as a statement of current views as to their pathogenesis.

Previous Descriptions of the Disease

Aran [1] in 1850 described the disease which we now call progressive muscular dystrophy under the title of *atrophie musculaire progressive*. Meyron [2] independently described the same disorder in 1852. There appears to have been no account before these in which progressive muscular dystrophy was distinguished from the muscular atrophies resulting from disease of the nervous system, although individual cases were noted by a number of previ-

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ous authors. Oppenheimer,[3] Duchenne,[4] Leyden and Moebius,[5] Erb,[6] Landouzy and Déjerine [7] and many others in the ensuing years added groups of cases, some of which had special characteristics. In 1879 Gowers [8] reported 44 cases from his own and his colleagues' experience and reviewed 176 cases from the literature in a monograph entitled "Pseudohypertrophic Muscular Paralysis." The English and German literature of that period uses this title rather regularly. Erb,[6] however, introduced the French term *Dystrophia musculaire progressiva* and since about the turn of the century most authors have called the group of disorders progressive muscular dystrophy.

Since the early twentieth century a number of additional types, thought to be distinguishable from the common form of progressive muscular dystrophy, have been described. These include an infantile variety and a type with initial atrophy beginning peripherally. The latter disorders are classified as dystrophies because of the presence of muscular weakness unassociated with other clinical or pathological signs of neurologic disease. They do not conform with common muscular dystrophies in the pattern of muscles involved nor in their manner of progression and are probably better considered as questionably related primary diseases of muscle. Other apparently related syndromes have been reported as single cases or in single family groups. Barnes,[9] for example, described lucidly and convincingly a type of adult muscular atrophy with associated obesity and pseudohypertrophy of muscle occurring in a single family. How often this disease occurs outside of the family he described is unknown. It must be extremely rare as no additional families have been reported. This apparent myriad of variants has produced a very confusing picture. Most recent authors [10, 11] have considered the differentiation of types unimportant in the consideration of their cases and have used the term progressive muscular dystrophy for the entire group.

No attempt will be made here to review all of the rather voluminous literature on the subject of muscular dystrophy. As it becomes pertinent in subsequent reports, this will be done. Shank et al.[10] and Hurwitz [11] have reviewed most of the important contributions in the recent past. Wilson's textbook of Neurology [12] supplies a great deal of accurate information about the clinical characteristics of these diseases.

Proposed Classification

About 250 patients with a variety of diseases primarily centering about muscular weakness have been examined by us in the past 18 months. About 175 of these presented signs which led to the diagnosis of progressive muscular dystrophy. Review of this clinical material has led to the conclusion that a simple and yet clinically satisfactory classification of muscular dystrophy can be devised and it is proposed to outline this tentatively here. The cases which have been seen can be divided into two homogeneous types which have the following characteristics. A detailed account of these cases,

together with evidence concerning their mode of inheritance, will be given in the papers which follow.

The *childhood* type of progressive muscular dystrophy begins in early childhood, nearly always affects males, is frequently inherited as a sex-linked recessive Mendelian trait, involves the axial and pelvic musculature initially, almost completely spares the facial muscles, is often accompanied by muscular enlargement (pseudohypertrophy), is rapidly progressive and is seldom compatible with survival to adult life. This type includes at least most of the patients previously described under the headings "pseudohypertrophic," "simple atrophic," "Duchenne" and "Leyden and Moebius" types.

The second or *facioscapulohumeral* type appears in late childhood or in adolescence, is characteristically inherited as a Mendelian dominant, thus affecting both sexes in approximately equal numbers, involves facial and pectoral girdle muscles initially, and is only rarely accompanied by muscular enlargement. Only a small percentage of affected persons are incapacitated before they are old. This group includes Erb's "juvenile dystrophy" and the type of "Landouzy and Déjerine."

Within a particular family the cases have remained true to this classification. The occasional case of presumed muscular dystrophy which has not fitted either of these types usually has been found to represent some other clinical entity, e.g., peroneal muscular atrophy or myotonia dystrophica. Three cases have been found in our series in which the clinical pattern was more like the progressive muscular dystrophies than any other disease but which did not fall readily into either the childhood or facioscapulohumeral type as defined here.

Two of these were girls in their twenties in whom the disease began in childhood but the muscular enlargement and the rapid progression seen in the childhood group were lacking. The third was a man of 56 who had pseudohypertrophy in his calves. His illness began in middle life with rather rapid progression to severe disability.

It need scarcely be stated that the distinction between the two types is based on clinical grounds alone. Nearly all cases of a large initial experience fit into it in spite of the rather restrictive definitions set up. That other groups may need to be differentiated is obvious from the few unusual cases already encountered. It would be desirable, as will become more obvious subsequently, to have some concept of the fundamental pathogenesis of the disorder on the basis of which an etiologically accurate classification could be devised. As yet we do not have any such information.

Inheritance

In the earliest descriptions of progressive muscular dystrophy it was recognized that the condition frequently is familial in character. A number of attempts have been made to define the nature of the inheritance. These studies have been of two general types. Many studies of small groups of

involved patients all belonging to one kindred have appeared. In most of these the conclusion was reached that the observed inheritance was consistent with a Mendelian dominant or a sex-linked recessive type. Other studies have been made of series of patients with the diagnosis presumably established on clinical grounds. In these all types of dystrophy were usually considered in a single category. These have led to the conclusion that the inheritance is very varied, including the following types: simple dominant, simple recessive, sex-linked recessive and other more complex hereditary mechanisms.

Julia Bell [18] summarized essentially all of the literature on inheritance of dystrophy up to 1943. Her report covered 1228 cases from the literature plus 113 new cases taken from the Case Books of the National Hospital, Queens Square, London, England, from 1926 to 1940. She included plates of over 300 pedigrees and summarized the clinical findings of the original authors carefully. Her monograph is a monumental source of information. However, her rather uncritical attempt to include all the cases described in the literature under the heading of dystrophy led her to a complex classification which we do not regard as either justified or necessary. Her classification included three genetic groups: (1) dominant, (2) recessive, and (3) sex-linked recessive; and three clinical groups: (*a*) pseudohypertrophic, (*b*) cases of atrophic muscular dystrophy characterized by wasting and weakening of affected muscles but with no history of enlargement and having no involvement of facial muscles, and (*c*) all cases in which the facial muscles were affected. She concluded that the same main gene can produce any of the above clinical types but that it is usual, although not invariable, for the same clinical type to be repeated in the same family. She assumed that the variation in expression of the trait results from other factors, environmental or genetic. She stated that pedigrees of dominant types are relatively rare. None had been encountered at the National Hospital during 14 years. It should be noted, however, that she accepted the data found in routine hospital admission family histories as the basis for this statement. Such information is almost completely useless in the careful evaluation of human inheritance.

The many other studies of the inheritance of progressive muscular dystrophy are less extensive than Bell's. Again, no attempt will be made to review them here but they will be discussed as they become pertinent in subsequent reports.

Pathogenesis

The primary abnormality in the disease appears to be localized in the muscle. Indeed it was the discovery at postmortem examination that few or no abnormalities were present in the nervous system which led to the delineation of progressive muscular *dystrophy* as separate from progressive muscular *atrophy* resulting from disease of the anterior horn cells of the spinal cord. All of this has been repeatedly confirmed and no other consistent anatomical anomalies have been found in autopsy material except

muscular atrophy, sometimes with fibrosis and replacement by fat. The microscopic lesions in the muscle are not specific, but Bowden and Gutman [14] were able to demonstrate that even the terminal intramuscular nerve fibers were intact in dystrophic muscle in contrast to their absence in the muscular atrophy resulting from neurologic disease. This apparent localization in the muscle of the pathologic process is also confirmed by the absence of the reaction of degeneration to electrical stimulation in progressive muscular dystrophy.

In the past, speculation concerning the pathogenesis of progressive muscular dystrophy has taken three general directions. One of the oldest views is the concept that this disorder is *always* heredito-familial and that therefore there is neither anything to be derived from speculating further about its mechanism nor is there any chance of modifying it except by eugenics. We are in general agreement with the premise but not with the conclusion. This will be discussed subsequently.

Another proposal has been that some poorly defined endocrine disturbance is responsible for the disorder. The evidence offered in support of this view is vague. Abnormalities of glucose metabolism have been reported. Various authors have observed attacks of hypoglycemia in progressive muscular dystrophy [15] and others have noted reduced glucose tolerance.[16] More careful investigation of carbohydrate metabolism has failed to support these concepts.[10] An abnormality in the pineal body was postulated by Timme [17] because of calcification seen in roentgenograms of the skull. On the basis of this observation and certain other data from the literature, including a case of so-called Fröhlich's syndrome with associated muscular dystrophy, he concluded that the muscular disease was the result of some imbalance of endocrine activity.

More valid support of the concept that progressive muscular dystrophy is related to a disturbance in endocrine function is the observation that at about puberty the rate of progress of the disorder tends to fall off sharply if it began in childhood. Indeed the only plausible reports of remission and "cure" [18] of progressive muscular dystrophy have been associated with the onset of puberty. One might emphasize, however, that genital and secondary sexual changes in patients with progressive muscular dystrophy take place quite normally. Consequently, any effect on the muscle disease, if present, must be an effect of the response of the end-organ, the muscle, to the sex hormones. Some encouraging reports are to be found about the therapeutic use of testosterone. However, such treatment has not been successful over prolonged periods.

An early proposal was that progressive muscular dystrophy results from an imbalance of sympathetic and parasympathetic activity. Kure [19] reported changes in the lateral gray matter of the spinal cord at levels corresponding to the areas of muscular atrophy. He claimed, in addition, that epinephrine and pilocarpine could be used as a means of successful treatment of the dis-

order. Like all other therapies suggested heretofore, this has not been found successful in the hands of other investigators.

It is apparent that the hypotheses we have discussed all suffer by the poor quality of the evidence on which they are based. One might well ask—what, if any, are the facts on which one might begin?

A line of attack on such a problem which has sometimes been successful has been to follow back from a known successful means of therapy to the pathogenesis. Unfortunately none of the many proposed regimens including glycine, endocrine preparations such as pituitary powder and testosterone, tocopherols, or pyridoxine and other vitamins, appear to have been successful if the reports are analyzed critically. Therefore, unless some fortunate accident should occur, the best means of approaching the problem of rational therapy for the disease is to try to discover its pathogenesis.

Two clear-cut phenomena which occur in progressive muscular dystrophy are worthy of emphasis. The pattern of muscular atrophy in progressive muscular dystrophy is a very characteristic one and unlike that seen in other disorders of muscle. In general, the axial muscles and proximal girdle muscles are involved before the distal girdle musculature. It is interesting that the former are the first muscles which are laid down in the embryo. In fact, a surprising degree of correlation of the order of onset of muscular involvement to the ontogenetic age of the muscles is found. For example, the pectoralis major arises as two parts. The sternal head appears very early in the embryo but the clavicular head appears much later. One of the best diagnostic signs in the patient with dystrophy is the persistence of the clavicular head of the pectoralis at a period when there is severe loss or absence of the sternal head. Bramwell called attention to these facts in 1925.[20]

A second observation which has been made consistently by all investigators is that excessive amounts of creatine are found in the urine. The cause of the creatinuria is not yet clear. Much new information is becoming available about the course of creatine metabolism [21, 22] in normal man. From this it may be possible to derive some more fundamental contrasts with the intermediary metabolism of creatine in the dystrophic.

Studies in recent years of the genetics of *Neurospora* [23] have shown that specific biochemical changes may occur in these organisms as the result of mutations of genes which are then inherited in typical Mendelian patterns. For example, a number of strains which require tryptophane in their media for normal growth have been found. Because the defects are at various stages in the course of the intermediary metabolism of tryptophane, these studies have shed new light on that subject as well as on the fundamental character of at least certain types of genetic determinants. It follows that a specific genetically determined deficiency in the metabolism of muscle may be the mechanism which leads to the atrophy of progressive muscular dystrophy. Thus the presumption that the fundamental mechanism is a genetic one does not rule out the possibility of modifiable abnormalities.

The fact that the muscles are intact at birth but atrophy in a symmetrical pattern related to the time at which they appear in the embryo suggests that the lesion might be one which develops with aging in a developmental sense. The synthesis, storage and intermediary metabolism of creatine, the myosin-actomyosin complex of reactions, the peptidases of muscle [24] and the carbohydrate cycle in muscle all suggest themselves as mechanisms which might be the site of a specific abnormality leading to muscular atrophy.

Summary

1. A brief review of previous studies of progressive muscular dystrophy is presented.

2. It is pointed out that two groups of progressive muscular dystrophy can be distinguished on clinical and genetic grounds: the childhood and facioscapulohumeral types.

3. Dystrophy frequently is a genetically determined disorder.

4. A peculiar pattern of muscular atrophy related to the age at which the anlage of a particular muscle appears in the embryo is found in progressive muscular dystrophy.

5. Creatinuria is the only well documented anomaly of metabolism which has been discovered in the patient with progressive muscular dystrophy.

6. No other data are available on which to start a search for the mechanism of the pathogenesis of this disease. A good argument for the existence of a specific biochemical lesion in the metabolism of the involved muscle can be developed.

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THE RESPONSE OF ACUTE LEUKEMIA TO THE ADMINISTRATION OF THE FOLIC ACID ANTAGONISTS, AMINOPTERIN AND A-METHOPTERIN: REPORT OF 14 CASES *

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Introduction

In June 1948 Farber et al.[1] presented a preliminary report on the therapy of acute leukemia in children, with the folic acid antagonist, aminopterin, 4-amino pteroylglutamic acid (N-[4-{2,4 diamino-6-pteridyl)-methyl] amino} benzoyl] glutamic acid). Of a group of 16 cases treated, five were reported in some detail. The latter were believed to have experienced temporary remissions. In February, 1949 in a follow-up report,[2] the senior author stated that approximately 60 cases of acute leukemia in children had been treated with aminopterin and other folic acid antagonists. Fifty per cent of this group of cases were reported to have shown some clinical improvement, but the details of these cases were not presented. Of the five patients described in the initial report, three had died at the time of the second report, while two were still living, 16 and 22 months since onset of illness, respectively. Dameshek [3] has recently presented a brief report on the treatment of 35 cases of acute leukemia in both adults and children with several folic acid antagonists. Nine patients in this group were said to have had "remissions" lasting from 2 to 8.5 months. Jacobson et al.[4] reported treating 10 patients with either aminopterin or a-methopterin (4-amino N-10 methylpteroylglutamic acid). One of seven patients treated with the latter drug was believed to have shown conspicuous clinical and hematological improvement. Of three patients treated with aminopterin, one was reported to have shown improvement. Pierce and Alt [5] briefly reviewed data accumulated in the treatment of 11 cases of acute leukemia over a period of two weeks to four months. Three of these patients died too soon after the institution of therapy to warrant inclusion in the review. Of the remaining

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eight patients, five were reported to have shown sufficient improvement to warrant the statement that they were in a temporary remission. Of a total of 43 cases of acute and chronic leukemia studied by Meyer [6] and a group of collaborators, only four were said to have shown any improvement. Wolman et al.[7] treated 10 children with acute leukemia with aminopterin over a period of two to six months. Seven remissions were reported.

Virtually all reports in the literature up to this time (June, 1949), have consisted of brief summaries of the total number of patients observed and treated by each group. In many instances, the period of observation was relatively short. With the exception of Meyers' report, most other investigators have reported a significant incidence of temporary remission in this hopeless malady. Because of the brevity of many of the reports, the criteria of remission have not always been stated.

It is the experience of virtually all clinicians who have observed significant numbers of patients with acute leukemia, that spontaneous temporary remissions, although quite rare, do, occasionally, occur. Often such spontaneous remissions seem to occur after the patient has experienced some complicating infection. The spontaneous remission rate reported by Diamond,[2] approximately 10 per cent of some 300 cases, seems to be somewhat higher than the general experience. Even rarer has been the occurrence of several spontaneous remissions in the same patient.

The fact that a number of competent observers have reported a significantly higher incidence of temporary clinical and hematological improvement in this uniformly fatal malady associated with the use of various folic acid antagonists, seems to make it imperative to continue to explore this avenue of investigation and to evaluate the data carefully. The authors have observed and treated 14 patients with acute leukemia with two folic acid antagonists, namely, 4-aminopteroylglutamic acid (aminopterin), and 4-amino, N^{10} methylpteroylglutamic acid (a-methopterin), from April, 1948 to the present (June, 1949). It is the purpose of this communication to present in some detail experiences gained in the therapy of these patients.

Clinical Data

The group of patients studied included six children, 11 months to eight years of age, two patients aged 15 and 17 years respectively, and six adults ranging in age from 26 to 63 years. There were six females and eight males in the group. In all instances, an effort was made on the basis of cytologic studies to determine the type of acute leukemia. Four patients were classified as acute myeloid leukemia; seven were of the acute lymphoid variety; and three were classified as acute monocytic. Although patients were observed in several hospitals, all blood studies were carried out by the same persons. Bone marrow aspirations were performed before the institution of therapy and at intervals throughout the period of observation. All patients received aminopterin, which was given in daily doses of 0.5 to 2.0

mg., intramuscularly. Some patients also received consecutive, but not concomitant, therapy with a-methopterin, which was given intramuscularly in daily doses of 2.0 mg. All patients received supportive therapy consisting of frequent blood transfusions and various antibiotics. Occasionally in an effort to combat drug toxicity, concentrated liver extract was administered coincidently with the continued use of the folic acid antagonist. In a few instances, the appearance of toxic signs led to the discontinuation of the folic acid antagonist and the temporary administration of intramuscular folic acid.

In analyzing the results, due consideration must be given to the influence of currently-used supportive measures, namely, the liberal use of blood transfusions and antibiotics. These measures, while undoubtedly useful in the control of some of the clinical aspects of the disease, do not, in the opinion of most observers, produce any significant hematological improvement. One cannot at this time assess the significance of the temporal prolongation of life. In evaluating the response to therapy, the following criteria were used. Complete temporary remission was considered to have occurred if both the peripheral blood and bone marrow demonstrated reversion to a normal pattern. This hematological improvement should be accompanied by a decrease in size of the lymph nodes and spleen, normal temperature, and a subjective feeling of well-being. A significant aspect of this clinical state would be the continued maintenance of a normal erythrocyte count, and hemoglobin level unaided by transfusions. In addition, the patient should maintain a normal platelet count. Partial temporary remissions would be represented by the achievement of some proportion of the above criteria. In some instances, patients demonstrated a clinical state of well-being which was not accompanied by significant hematological improvement. These were not considered remissions in any way.

The following case reports are not presented in chronological order.

Case Reports

Case 1. R. H.,* a 39 year old white, single, female clerical worker, was admitted to the hospital on June 27, 1948. She had been in good health until March 1938 when she first began to complain of weakness, fatigue, occasional mild "dizzy" spells, and pains in the hips. These symptoms became progressively worse and in May, afternoon elevations of temperature began to occur. On June 20, the patient was admitted to another Baltimore hospital where a diagnosis of acute myeloid leukemia was made and she was transferred to the University Hospital. Review of the systems revealed many complaints of a chronic anxiety nature such as episodes of tachycardia and functional gastrointestinal disturbances. The past history revealed that the patient had had a supravaginal pan-hysterectomy in 1941 following which she received estrogen therapy for approximately a year for menopausal symptoms.

On physical examination she was observed to be a well developed, well nourished white female of a distinctly masculine habitus. There was marked pallor of the skin and mucous membranes. Enlarged lymph nodes were present in the anterior cervical chain and in the submaxillary and submandibular regions. Considerable pyorrhea alveolaris was noted about the few remaining teeth. Heart and lungs were essentially

* This patient was studied through the courtesy of Dr. Frank Geraghty.

negative. The liver and spleen were both palpable three to four fingers'-breadth below the costal margins. A well healed lower midline abdominal scar was present. Remainder of the physical examination was within normal limits.

Laboratory Studies: Red blood cells: 3.70 million; hemoglobin: 10.8 gm.; white blood cells: 4,400; platelets: 59,200. Differential white count revealed 69 per cent lymphocytes, 16 per cent 'blasts, 9 per cent polymorphonuclear neutrophiles, 5 per cent myelocytes, and 1 per cent monocytes. Routine urine and stool examinations were negative. The serological test for syphilis was negative. Blood urea nitrogen and sugar were normal. The blood uric acid level determined on several occasions was found to be 7.6 mg. per cent and 8.9 per cent. Bleeding time, clotting time (Lee-White), prothrombin time (one-stage Quick method) and clot retraction were normal. Roentgen-rays of the chest and long bones were negative. An electrocardiogram was negative. Sternal bone marrow examination revealed 87 per cent of the cells to be undifferentiated 'blasts; there were also 9 per cent normoblasts, 1 per cent pronormoblasts, 2 per cent lymphocytes, 1 per cent granulocytes. The marrow was markedly hypercellular and many of the 'blast cells were in various stages of mitosis. The diagnosis of acute leukemia, probably myeloid, was confirmed by subsequent studies.

Course: The patient was started on 2 mg. of aminopterin intramuscularly daily on June 28, 1948 and continued on this dosage for eight days. During this period symptoms of an acute respiratory infection developed, and there were several spontaneous nose bleeds as well as various purpuric manifestations in the skin and mucous membranes. Because of an increasing hemorrhagic tendency, aminopterin was discontinued and the patient was given 15 mg. of folic acid per day for several days. During this period the patient had been receiving intramuscular penicillin and frequent transfusions. Aminopterin in doses of 1 mg. per day was then resumed for another period of five days. At the end of this time there was an increase in the hemorrhagic diathesis, diarrhea appeared, fever was more marked, and physical signs of a right lower lobe pneumonitis were noted. The patient appeared almost moribund.

In an effort to control the bleeding tendency toluidine blue, 3.0 mg. per kilogram, was given intravenously in physiological saline solution on several successive days. The diarrhea became increasingly severe and many of the stools contained gross blood.

Diffuse ulcerative stomatitis developed and the patient became moderately icteric. Folic acid, 45 mg. per day intramuscularly, was resumed at this time in an effort to counteract what were thought to be evidences of aminopterin toxicity.

At the height of this extremely critical clinical picture, it was noted that certain significant hematologic changes were taking place (figure 1). Bone marrow examination on July 13 revealed a marked decrease in cellularity as compared to the pre-treatment marrow. 'Blasts had decreased to 10 per cent and the remaining cells consisted of 25 per cent lymphocytes, 7 per cent granulocytes and 58 per cent erythroid elements. Peripherally, the leukocyte count dropped to 450 cells per cubic mm., and during the next six days ranged between 650 and 1,200. The red blood cell count was maintained at 4 to 4.71 million with repeated transfusions. Polymorphonuclear neutrophiles which were only 4 per cent on July 13, rose steadily to 90 per cent by July 22, while the lymphocytes progressively dropped from 96 per cent to 10 per cent. No 'blasts had been observed in the peripheral blood from July 6 onward. Platelet counts which had been as low as 4000 per cu. mm. gradually rose to 284,200 per cu. mm. on July 29.

Marked improvement in the clinical picture began to occur. All evidences of aminopterin toxicity disappeared. (The total dose had been 21.0 mg. from 6/28/48 to 7/13/48.) Folic acid, 45 mg. per day, which had been started on 7/18/48 was discontinued on 7/23/48. Thereafter, therapy consisted only of 600,000 units of penicillin daily. After July 24, the erythrocyte level remained above 4.5 million

without further transfusions. The only evidence of drug toxicity observed at this time was a rather definite, diffuse, but partial, alopecia. Another bone marrow examination was made on July 27, 1948 which revealed normal cellularity and a differential count as follows: 0.5 per cent myeloblasts, 8.5 per cent myelocytes, 20 per cent neutrophilic metamyelocytes, 31 per cent segmented neutrophiles, 26 per cent lymphocytes and 14 per cent erythroid elements. Except for the slight increase in lymphocytes the picture was that of a normal marrow and was in sharp contrast to the very hypercellular marrow consisting almost entirely of 'blasts observed before therapy. By August 3, the patient was so well clinically and hematologically that she was allowed to leave the hospital. On that date the blood picture was as follows: White blood cells: 3,050; red blood cells: 4.55 million; hemoglobin: 12.7 gm.; plate-

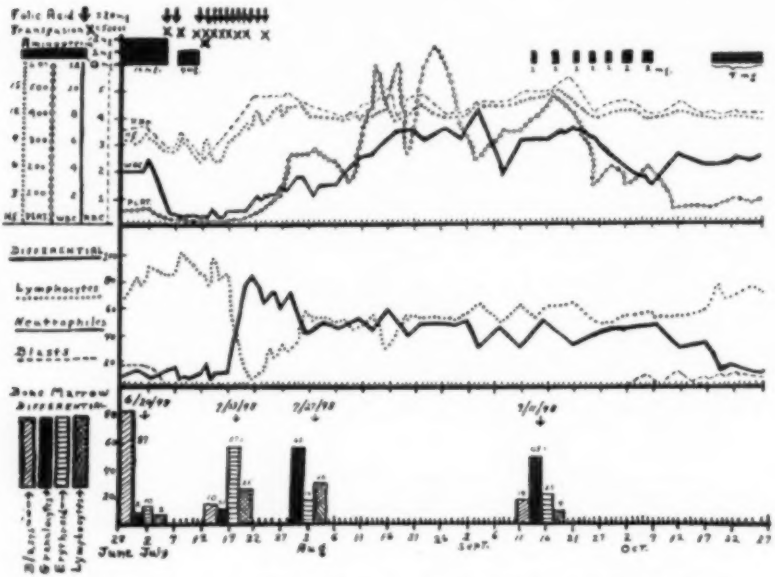


FIG. 1. *Case 1.* Hematological studies in a patient with acute myeloid leukemia treated with aminopterin.

lets: 299,200. Differential count showed 50 per cent neutrophiles, 49 per cent lymphocytes and 1 per cent basophiles. In summary, during the period of hospitalization, the patient received a total dosage of 21 mg. of aminopterin, 400 mg. of folic acid and 6,000 c.c. of whole blood.

From August 3 to September 3, 1948 she was in a definite state of remission. No specific therapy was employed. The patient gained weight, remained afebrile and was quite active physically. During this time, the alopecia, first noted in the hospital, became more striking. Blood studies were made at frequent intervals and during September began to show distinct deviations from normal consisting, in the main, of a gradually diminishing proportion of granulocytes and a corresponding increase in mature lymphocytes (chart 1). Bone marrow examination on September 11, displayed a significant rise in 'blasts to 19 per cent of the differential myelogram. In

spite of these changes the patient's clinical state remained so satisfactory that she was permitted to resume her clerical work for part of each day. On September 17, aminopterin, mg. 1.0, twice weekly, was resumed. On October 1, the dose was increased to 2.0 mg. twice weekly. Approximately one week later immature forms were noted again in the peripheral blood and the platelet count diminished significantly. Slight

TABLE I

Peripheral Blood Studies, Case 14, Acute Lymphoid Leukemia, Treated with Aminopterin

Date 1949	WBC	RBC	Hgb. Gm.	PMN	Eos.	Bas.	Mon.	Lym.	Young Lymph.	Blasts	Myelocytes		Platelets	Blood Transfusion
											A & B	C		
4/12	33,550	0.91	3.0	11	0	1	0	57	9	20	0	2	6,800	160 c.c.
4/13	15,550	1.78	5.3	18	0	1	1	45	13	21	0	1	—	165 c.c.
4/14	3,450	2.53	7.8	24	0	0	0	54	10	12	0	0	2,500	—
4/15	4,350	—	7.4	13	0	1	2	63	8	12	0	1	—	—
4/16	5,200	3.50	11.0	7	1	0	1	76	5	10	0	0	—	160 c.c.
4/18	4,100	—	12.8	3	2	3	1	88	2	1	0	0	—	—
4/19	5,350	—	13.2	5	2	2	1	76	6	3	0	0	—	—
4/20	5,300	4.55	13.6	7	0	3	1	82	4	3	0	0	4,500	—
4/22	8,300	4.44	13.3	26	2	4	0	65	1	1	0	1	4,400	—
4/23	6,800	—	12.7	28	2	2	0	68	0	0	0	0	—	—
4/25	6,400	—	11.6	12	1	1	0	81	3	2	0	0	—	—
4/26	5,950	4.13	11.5	24	3	1	0	68	1	2	0	1	41,000	—
4/27	3,450	—	10.8	28	0	2	0	70	0	0	0	0	—	—
4/30	3,150	3.69	10.9	16	2	0	0	82	0	0	0	0	—	160 c.c.
5/2	3,000	3.55	9.0	6	4	0	0	88	2	0	0	0	—	—
5/3	2,050	3.62	9.9	21	6	1	0	69	1	0	0	0	3,600	150 c.c.
5/5	1,400	3.55	9.6	38	0	0	2	60	0	0	0	0	3,500	350 c.c.
5/6	1,700	—	10.0	36	2	0	4	58	0	0	0	0	—	230 c.c.
5/7	1,350	—	10.8	30	2	0	0	68	0	0	0	0	3,700	200 c.c.
5/9	2,100	4.76	14.2	37	1	0	0	51	0	0	4	7	19,400	300 c.c.
5/10	3,350	5.01	15.1	41	2	0	2	38	0	0	5	12	145,000	—
5/11	4,850	5.23	14.9	30	3	1	1	32	0	0	17	16	260,000	—
5/12	4,440	5.15	14.6	50	5	0	1	26	0	0	4	14	346,800	—
5/13	6,250	5.13	13.8	44	6	1	0	24	2	0	0	23	530,400	—
5/14	6,800	—	15.6	32	0	0	5	29	0	0	2	12	—	—
5/16	6,700	5.23	13.4	55	3	0	1	31	0	0	0	10	780,000	—
5/17	7,050	5.35	14.0	62	0	0	0	26	0	0	0	11	784,400	—
5/18	7,450	—	13.2	61	0	0	0	33	0	0	0	2	—	—
5/19	6,600	5.16	12.8	61	1	0	3	33	0	0	0	2	—	—
5/20	9,300	—	12.1	71	0	0	3	25	0	0	0	1	958,000	—
5/21	11,400	—	14.0	66	0	1	3	29	0	0	0	1	—	—
5/23	7,200	5.19	13.5	77	0	1	1	20	0	0	0	1	846,600	—
5/24	7,500	—	12.8	61	0	2	4	31	0	0	0	2	—	—
5/25	10,500	—	12.7	62	1	1	3	33	0	0	0	0	—	—
5/26	6,950	—	12.7	55	1	0	4	35	0	0	0	5	—	—
5/27	10,400	5.14	13.0	75	1	1	1	22	0	0	0	0	703,800	—
5/30	11,100	5.21	13.2	50	1	1	3	45	0	0	0	0	1,060,000	—
6/2	8,940	4.92	12.2	53	3	1	5	38	0	0	0	0	—	—
6/7	8,150	4.44	13.0	39	11	0	5	45	0	0	0	0	509,000	—
6/14	7,950	4.45	11.9	37	5	3	5	50	0	0	0	0	660,000	—
6/21	8,300	4.70	13.0	54	10	1	2	28	1	2	0	2	564,000	—

afternoon elevation of temperature began to occur; the patient complained of increased fatigability and a few purpuric and petechial hemorrhages were noted scattered over the skin.

The reappearance of slight diarrhea on October 8 led to discontinuance of aminopterin after a total dose, during this 21 day period, of 10 mg. Sudden blurring

of vision in the left eye occurred on October 14 and was found on ophthalmoscopic examination to be due to edema of the retina rather than hemorrhage. The patient was re-admitted to the hospital at this time. Study of the blood picture demonstrated changes again characteristic of acute leukemia. From October 20 to 26, the patient received 0.5 mg. aminopterin daily without any hematological or clinical change. This dose was increased to 1.0 mg. daily from October 27 to November 2, but still no improvement was observed. As a matter of fact, the clinical picture now was dominated by an increasing hemorrhagic diathesis. Because of the re-appearance of diarrhea, aminopterin was discontinued after a total dose of 11 mg. An effort was made to control the diffuse hemorrhagic phenomena with toluidine blue, intravenously, in a dose of 3.0 mg./kg., but without success. In spite of numerous transfusions, the patient went into what appeared to be typical hemorrhagic shock and died on November 10. Permission for autopsy could not be obtained.

Comment: The total duration of illness in this patient was approximately seven months. Following the administration of 21 mg. of aminopterin improvement in both the bone marrow and peripheral blood pictures was observed. These changes occurred at a time when the patient had physical signs of bilateral pneumonitis as well as evidences of severe toxic reaction to the drug, consisting of diarrhea, stomatitis, alopecia and icterus. For 81 days, she remained clinically and hematologically in remission without further specific therapy. Bone marrow examination at the end of this period demonstrated the re-appearance of blasts and significant abnormalities of the leukocytes in the peripheral blood recurred. In spite of the reinstitution of therapy, the subsequent course was rapidly downward and was characterized, terminally, by an uncontrollable hemorrhagic diathesis.

Case 2. I. B., a 16 year old white, female student, was admitted to the hospital on June 6, 1948. Five weeks before, she had begun to experience vague intermittent pain in the left lower extremity. Three weeks before admission severe aching in both thighs and hip joints developed and was associated with headaches and "dizzy spells." Marked pallor was noted by her parents. The family physician made a diagnosis of "rheumatism" and ordered the patient to remain in bed. There was apparently no fever at this time. She was subsequently seen by another physician who advised admission to the Washington County hospital. Here she received eight whole blood transfusions. The pains in the thighs and hips subsided sufficiently to permit discharge from the hospital on June 1, 1948. For several days she felt quite well, but on June 3, symptoms returned and at this time she also had a severe spontaneous nose bleed. She was readmitted to the same hospital and again received three whole blood transfusions. A diagnosis of acute myeloid leukemia was made and the patient transferred to the University Hospital. The past history, family history, and review of symptoms were all non-contributory.

Physical examination revealed a well developed, well nourished white female in no acute distress. There was marked pallor of the skin and mucous membranes. Several small shotty lymph nodes were observed at the angles of the jaw. The heart and lungs were normal. There was a small hard elevation, the size of an olive, firmly attached to the sternum in the midline at the third interspace. This was said to have appeared following a previous sternal puncture. Liver and spleen were not palpable. The remainder of the physical examination was within normal limits.

Laboratory Studies: Red blood cells: 4.56 million; hemoglobin: 13.3 gm.; white blood cells: 7,000; platelets: 27,000. Differential: neutrophiles 33 per cent; lymphocytes 39 per cent, monocytes 2 per cent, myeloblasts 1 per cent, promyelocytes 19 per

cent and myelocytes 7 per cent. Routine urine and stool examinations were negative. Serological test for syphilis was negative. All blood chemical studies were within normal limits. Roentgen-rays of the chest and long bones were negative. Numerous liver function studies, prothrombin estimations, bleeding and coagulation times were all normal. Sternal bone marrow revealed a marked increase in cellularity and the following differential count: 25.6 per cent myeloblasts, 19.3 per cent promyelocytes, 17.3 per cent myelocytes, 20.3 per cent metamyelocytes, 1 per cent segmented neutrophiles, 16.2 per cent pronormoblasts. The diagnosis of acute leukopenic myelogenous leukemia was confirmed.

Course: Aminopterin 2.0 mg. intramuscularly per day was begun on June 7. After 12 mg. of the drug had been given, the patient began to complain of "soreness of the mouth and gums." Aminopterin was reduced to 1.0 mg. daily and liver extract 10 units, intramuscularly, daily, was given. In spite of this regime, the stomatitis increased with the lesions extending to the upper and lower lips. These appeared first as small raised reddened areas, which later became indurated and inflamed. The centers soon became necrotic and formed deep ulcerations. The craters were covered with a dirty white, foul smelling membrane. Because of severe epistaxis, it was necessary to give her 2,000 c.c. of blood over a period of three days. The platelet count fell to 4,000. The total dose of aminopterin from June 7 to June 22 was 21 mg. On the latter date the drug was discontinued because of toxic manifestations and 20 mg. of folic acid per day were given for three days. Aminopterin, 1.0 mg. per day, was resumed on June 25. On June 30, 1948, the white blood count was 15,500, the red blood count 4.83 million; hemoglobin 12.9 gm.; platelets 7,600. Differential: neutrophiles 28 per cent, lymphocytes 13 per cent, promyelocytes 4 per cent and myelocytes C 55 per cent. The patient felt fairly well, had a good appetite, and was allowed up. There was slight afternoon fever to 99 or 100° F. The most significant change at this time was the disappearance of 'blasts from the peripheral blood and the increasing presence of myelocytes of the "C" type.

During the first three weeks of July, the patient had no complaints and appeared clinically well. She continued to receive 1:0 mg. of aminopterin daily plus 10 units of liver extract, and felt well enough to assist the nurses on the ward. Blood counts revealed a significant rise in mature segmented neutrophiles (figure 2). A typical blood picture is the one of July 17: Red blood cells: 3.41 million; hemoglobin: 8.9 gm.; white blood cells: 5,800. Bone marrow examination on July 10, 1948 showed slight improvement, indicated by moderate reduction in myeloblasts and a corresponding increase in mature granulocytes. By the end of July, definite diffuse alopecia was observed. The course was further marked by the appearance of intercostal herpes zoster and a urinary tract infection. The latter responded to streptomycin therapy. During June and July, the patient received a total of 64 mg. of aminopterin.

During August, the patient continued to receive 1.0 mg. of aminopterin daily. Recurrence of the urinary infection necessitated the administration of streptomycin. In spite of the reappearance of mild diarrhea, aminopterin therapy was maintained. Increasing alopecia was evident and there was marked anorexia and weight loss of 10 lbs. A series of red, tender, indurated nodules resembling lesions of erythema nodosum appeared on the left leg. It was necessary to give 3,000 c.c. of whole blood during August. The blood count of August 30 is fairly representative of the situation during this month: Red blood cells: 4.05 million; hemoglobin: 10.2 gm.; white blood cells: 3,450; platelets: 4,000. Differential: 52 per cent neutrophiles, 26 per cent lymphocytes, 4 per cent promyelocytes and 18 per cent myelocytes. Bone marrow examination on August 10 revealed no essential change from the pre-treatment picture. By the end of August, the patient had received a total dose of 95.0 mg. of aminopterin.

Early in September severe epistaxis and other hemorrhagic phenomena led to

the discontinuance of aminopterin for approximately two weeks. On September 15, another analogue of folic acid, a-methopterin, was begun in doses of 2.0 mg. intramuscularly daily and continued for eight days. During this time increasing immaturity of the granulocytes in the peripheral blood was noted. This drug was discontinued after a total dose of 16 mg. had been given and aminopterin, mg. 1.0 daily was resumed for eight days. The course during September was characterized by recurrence of pyelonephritis and numerous episodes of epistaxis which were difficult to control.

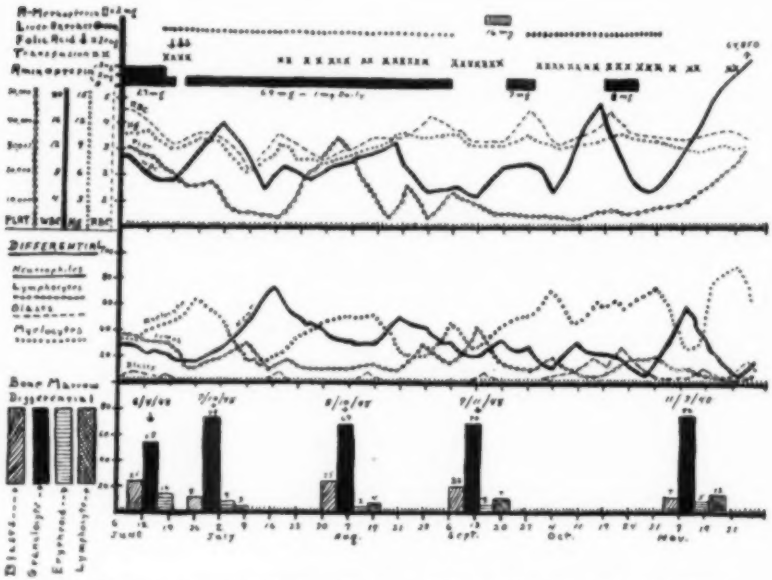


FIG. 2. *Case 2.* Hematological studies in a patient with acute myeloid leukemia treated with aminopterin.

Aminopterin was again discontinued on October 1, 1948. Recurrence of hemorrhagic manifestations required heroic therapy. Blood had to be administered daily. Because of persistent anorexia, parenteral alimentation was resorted to. In spite of these efforts marked weight loss continued, and with the increasing alopecia, the patient developed a distinctly cadaverous appearance. Several decubitus ulcers appeared over bony prominences. The blood picture showed an increasing number of myeloblasts. From October 15 to 22, the patient again received aminopterin mg. 1.0 daily without noticeable effect on the peripheral blood. On October 22, clinical and roentgenological signs of pneumonitis at the left base appeared. Death appeared imminent on numerous occasions during this period.

The blood picture in early November displayed a remarkable shift in the differential white count even though no aminopterin was being given. The picture of November 6 is typical: Red blood cells: 3.50 million; hemoglobin: 9.3 gm.; white blood cells: 800; platelets: 6,800. Differential: 58 per cent segmented neutrophiles; 11 per cent lymphocytes, 5 per cent promyelocytes and 26 per cent myelocytes. Bone marrow examination for the first time revealed marked improvement. It was much

less cellular than on admission and showed a great increase in metamyelocytes and segmented neutrophiles. Only 7 per cent of the cells were myeloblasts, 9 per cent promyelocytes and 20 per cent myelocytes, while 47 per cent were segmented and non-segmented neutrophiles. There were 12 per cent lymphocytes and 5 per cent erythroid elements. Nevertheless, from this date onward the peripheral blood picture began to deteriorate again. On November 20, aminopterin therapy was resumed. Quite suddenly on November 23, the patient went into shock and died. An autopsy was performed.

Autopsy findings were quite characteristic of acute leukemia. No significant changes which could be specifically attributed to aminopterin were noted.

Comment: The total duration of illness in this patient was approximately eight months. During the entire period of observation, the picture was typical of an aleukemic or leukopenic type of acute myeloid leukemia. From June 6 to November 23, with the exception of several brief intervals, she was almost constantly under treatment with a folic acid antagonist. In all, during this time she received 114 mg. of aminopterin and 16 mg. of a-methopterin. Other important aspects of the therapeutic management were the continuous use of various antibiotics and the liberal use of whole blood. Folic acid was given for only three days during the entire period of hospitalization. However, concentrated liver extract, 10 units per day, was administered virtually throughout the entire time. Although there were moderate changes for the better in both the peripheral blood and bone marrow at various times during the six month period of observation, no definite remission can be said to have occurred. Various evidences of drug toxicity appeared from time to time, but did not necessitate discontinuance of the medication except for brief intervals. A very striking aspect of the clinical picture was marked terminal cachexia closely resembling that seen with advanced malignancy.

Case 3. A. L.,* an eight year old white male was admitted to the Sinai Hospital on June 25, 1948 complaining of fever and weakness of three months' duration. Pain in the knees and increasing afternoon elevation of temperature were first noted two weeks prior to admission. Numerous episodes of epistaxis occurred during this time and the parents had observed unsteadiness in the child's gait.

Review of the past history revealed that at the age of six the patient had had a prolonged episode of temperature elevation and fatigability, which was associated with a primary pulmonary tuberculous complex and the development of a positive tuberculin patch test. Within six months this lesion apparently became quiescent. There was a history of frequent nightsweats during the past three years and occasional episodes of epistaxis during the three months preceding admission. Family history and history by systems was otherwise negative.

Physical examination on admission revealed a pale, lethargic youngster whose temperature was 103° F. The cervical and inguinal lymph nodes were moderately enlarged. Heart and lungs were normal. The liver was felt one finger's breadth below the costal margin and was slightly tender. The spleen extended three fingers' breadth below the costal margin and was smooth and non-tender. Numerous ecchymoses were observed on both lower extremities. The remainder of the examination was essentially negative.

* The patient was studied through the courtesy of Dr. Aaron Harris.

Laboratory Studies: Red blood cells 2.50 million; hemoglobin: 8.7 gm.; white blood cells: 7,600; platelets: 118,000. Differential count: 86 per cent lymphocytes (no 'blasts recognized), and 14 per cent granulocytes. Routine urine and stool examinations were negative. Serology for syphilis was negative. Blood cultures and blood chemical studies were all within normal limits. Roentgen-ray of the chest showed an ill-defined haziness in both bases. Hematological consultation several days after admission and review of the blood smears revealed the following differential: 21 per cent lymphoblasts, 70 per cent lymphocytes, and 8 per cent granulocytes. Sternal bone marrow on June 28, 1948 demonstrated 99.6 per cent of the cells to be in the lymphoid series, with 33.6 per cent lymphoblasts; 0.2 per cent granulocytes, and 0.2 per cent erythroid elements. A diagnosis of acute lymphatic leukemia was made.

Course: This patient was started on 1.0 mg. of aminopterin daily on June 30, and was given almost daily transfusions. After he received 8.0 mg. of the drug, the total white count fell to 600 cells on July 10. The drug was discontinued and the patient given 10 mg. of folic acid daily for four days. During this time, lymphoblasts in the peripheral blood smears ranged from 15 to 30 per cent of the differential. In spite of transfusions the red cell count remained low and the clinical picture was unchanged. On July 4, 1948, the patient was placed on 400,000 units of penicillin daily. In spite of the fact that no additional aminopterin had been given after July 7, by the middle of the month he began to show remarkable improvement. The appetite improved, weight increased and the spleen was markedly reduced in size, to a point where it was barely palpable. On July 15, aminopterin in daily doses of 0.5 mg. was resumed. Approximately one week later, the peripheral counts began to show more granulocytes and less lymphoblasts (figure 3). The red cell count was maintained between 4 and 5 million without transfusion, and platelet counts rose to normal and remained so for more than a month. Concomitantly, the lymph nodes diminished in size and the patient became afebrile. He was allowed to be up and about on the ward and subjectively felt quite well. Sternal bone marrow on July 27 was markedly improved and revealed the following differential: 33.5 per cent granulocytic elements, 12.5 per cent erythroid elements and 53.7 per cent lymphoid elements, with a reduction of lymphoblasts to 9.5 per cent. The marrow was distinctly less cellular than on previous examination.

By early August, the granulocytes in the peripheral blood smear had risen to 84 per cent and no 'blasts were present. Total white count was 7,850 and the platelets 330,000. The patient was considered to be showing a clinical and hematological remission. He had received, by this time, a total dose of 23.0 mg. of aminopterin. On August 10, a few small ulcers were noted on the buccal mucous membranes and aminopterin was therefore discontinued for five days. Coincident with this change in regime the white count rose from 8,850 to 40,450 and 22 per cent lymphoblasts were noted in the peripheral blood smears. Aminopterin, in doses of 1.0 mg. daily was resumed on August 15, but the white count continued to rise and reached 56,000 by August 20. A coincidental drop in the red count and hemoglobin was observed. In spite of therapy, the percentage of 'blast cells continued to increase. The platelet count remained between 2–300,000, but a number of petechiae were observed on the extremities, and the bleeding time increased to 28 minutes. Despite numerous transfusions, the anemia became more pronounced. The total white count dropped to normal levels, but immature forms persisted. The liver, spleen and lymph nodes began to enlarge slowly. Despite continuous antibiotic therapy, daily elevations of temperature occurred. Severe epistaxes began to occur so frequently that nasal packing became necessary on August 29.

Purpuric and ecchymotic lesions appeared over the entire body. Between August 30 and September 6, he received 5,500 c.c. of whole blood. For three consecutive

days, beginning September 3, toluidine blue, mg. 75, was given intravenously without any effect upon the hemorrhagic state. Bleeding occurred, literally, "from every pore." On the morning of September 8, 1948, he suddenly began to complain of a severe intractable frontal headache. That afternoon, a sudden tonic convulsion occurred and shortly thereafter he died. Permission for autopsy was granted.

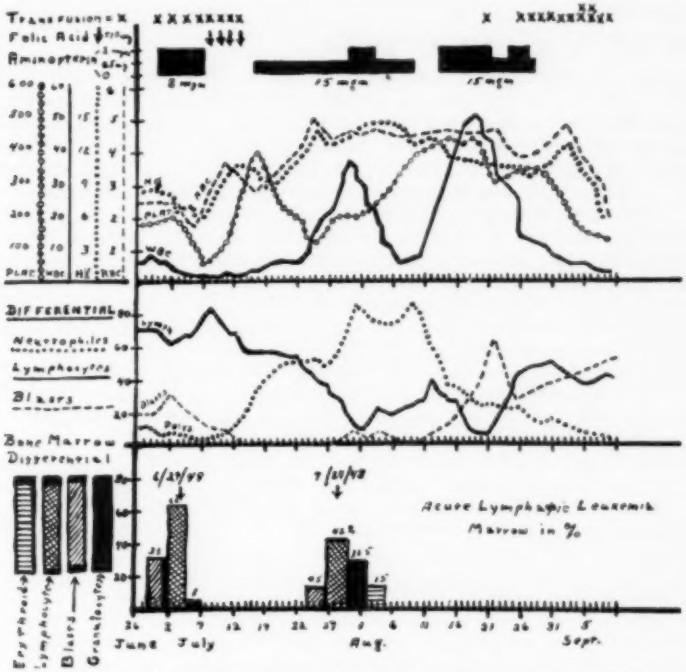


FIG. 3. *Case 3.* Hematological studies in a patient with acute lymphoid leukemia treated with aminopterin.

The autopsy revealed extensive hemorrhages throughout the viscera. Evidence of an agonal *Cl. welchii* septicemia was observed. Multiple shallow ulcers of the esophagus and small intestine were noted. Histologically, a picture characteristic of acute leukemia was observed. The only lesions possibly attributable to specific drug therapy were the gastrointestinal ulcerations.

Comment: This patient with acute lymphoid leukemia was ill for approximately five and one-half months. For some 10 weeks he was under constant observation and therapy in the hospital. After receiving 23 mg. of aminopterin, there was unquestionably a partial clinical and hematological remission. However, even during this period the bone marrow revealed a small, but significant, number of lymphoblasts. Other objective evidences of remission included definite reduction in size of the spleen, liver and lymph

nodes. The subjective improvement was noteworthy. Because of the appearance of some buccal ulceration, aminopterin was discontinued for five days. At the end of this period increased clinical and hematological manifestations of leukemia were noted. One is tempted to think of the leukemic state as, figuratively, having been kept at bay during specific treatment. The reinstitution of therapy was without effect. The terminal picture was characterized by uncontrollable bleeding.

Case 4. J. H.,* 17 year old, white male student was admitted to the hospital on July 18, 1948, with the following history. He was in good health until the first of June, 1948, when he developed pain in the left upper quadrant of the abdomen following the lifting of a heavy object. Shortly thereafter, he began to feel listless, fatigued easily, and lost his appetite. Afternoon elevations of temperature began to occur. These symptoms continued for approximately one month, during which time he lost 10 lbs. in weight. Ten days before admission, while playing billiards he developed pain in both wrist joints, especially marked on the right. Persistence of joint pain led him to consult a physician who found his temperature elevated and ordered him to bed. During the next five days additional joints became involved, and bone tenderness was noted. Blood studies revealed a marked anemia and a leukocyte count of 200,000. Hospitalization was advised and accepted. The past, family and system histories were essentially negative.

Admission physical examination revealed a well nourished, well developed, white male. The temperature was 102° F. There were several non-tender, firm, discrete lymph nodes, 1 to 2 cm. in size, in the cervical areas, and small shotty nodes in both axillae. The lungs were clear and examination of the heart was negative. The edge of the spleen could be felt three fingers'-breadth below the costal margin and extended considerably toward the mid-line. Slight bilateral inguinal adenopathy was present. Although no joint swellings were present, motion was limited due to extreme pain. Pressure over the forearms, legs and wrists elicited pain. The remainder of the examination was negative.

Laboratory Studies: Red blood cells 3.34 million; hemoglobin: 10.2 gm.; white blood cells 230,000; platelets: 60,120. Differential white count showed 98 per cent of the cells to be of the lymphoid series and of varying degrees of maturity; the remaining 2 per cent were segmented neutrophiles. Repeated routine urinalyses were negative. Blood chemical tests revealed no abnormalities. All other studies were within normal limits. Sternal bone marrow examination on July 20 revealed 97.8 per cent of the cells in the lymphoid series. Ten per cent of these were lymphoblasts, and the remainder were more mature lymphocytes. Normoblasts constituted 0.4 per cent of the differential count and granulocytes, 1.6 per cent. The findings were compatible with a diagnosis of acute or subacute lymphatic leukemia.

Course: Frequent transfusions and intramuscular penicillin formed the mainstay of therapy during the first 24 days of hospitalization. Bone and joint pains were extremely incapacitating, any movement producing excruciating pain. Some joint swelling was observed during this period. Large doses of a variety of analgesics and opiates were necessary to achieve relief. The temperature rose each day as high as 103° F. During this period, the total white count fell spontaneously to a level of 40,000, but the platelets remained quite low and the anemia persisted.

Aminopterin 1.0 mg. daily intramuscularly was begun on August 10, 1948, the twenty-fourth day of hospitalization. At that time, the white count was 22,000, the red count 2.07 million; hemoglobin: 6.4 gm. The differential white count revealed 98 per cent lymphocytes and 2 per cent neutrophiles. Platelets were 33,120. After

* This patient was studied through the courtesy of Dr. H. Raymond Peters.

three doses of aminopterin, the acute pain in the joints disappeared and within five days the swelling receded and the patient was able to get out of bed and sit up for the first time in a month. The white count fell to 3,950 and the dosage of aminopterin was reduced to 0.5 mg. daily on August 16, 1948. A slight glossitis and stomatitis appeared two days later but disappeared in a few days with no change in therapy. By August 21, 1948, eleven days after aminopterin was started, the spleen had receded in size to a point where it was just palpable at the costal margin. The patient was quite comfortable and did not require any analgesics at this time. A slight increase in the proportion of granulocytes in the peripheral blood was observed. Transfusions continued to be necessary and at no time did the platelets show any tendency to rise. Slight daily elevation of temperature continued.

The white blood counts varied between 2,000 and 4,000 for 13 days, but little change was noted in the differential counts. He continued to feel well and was able to be up and about until September 5, when he began to complain of severe pain in the left hip and thigh. Four days later, he began to complain of pain in the right thigh and right wrist. Increasing afternoon peaks of temperature were observed. A few small ulcers appeared on the tip of the tongue. On September 9, since no significant changes had been observed in the peripheral blood or bone marrow, therapy was changed to a-methopterin, 2.0 mg. daily. On the following day, the patient became nauseated and began to vomit. Vomiting persisted and the patient began to complain of severe, diffuse, lower abdominal pain. The abdomen became somewhat rigid that evening and the temperature rose to 104° F. It was felt that the patient had either developed peritonitis or a hemorrhagic effusion into the peritoneal cavity. A definite icteric tint appeared on September 11, and steadily deepened. Hematemesis occurred at this time also. He lapsed into coma and died later that evening. No autopsy was obtained. The patient had received a total of 18 mg. of aminopterin and 6 mg. of a-methopterin over a period of 32 days.

Comment: The most striking clinical aspect of this case was the very marked bone and joint pain. Frequent large doses of opiates were required to partially control these symptoms. After the administration of approximately 5 mg. of aminopterin, striking improvement in the skeletal pain occurred. For some four weeks, the patient showed marked subjective improvement but no corresponding changes in the bone marrow or peripheral blood. However, during this time definite reduction in the size of the spleen was noted. In view of the lack of response to aminopterin, the patient was treated for a brief interval with a-methopterin receiving, however, only 6 mg. of this drug before death. It was felt that some acute intraabdominal accident was responsible for the rapid termination of the disease. Aside from temporary improvement in skeletal pain, the response to specific therapy had been minimal.

Case 5. W. W.,* a 37 year old white male physician (dermatologist), was admitted to the hospital, March 13, 1948 complaining of "sore throat and malaise" of three weeks' duration. The patient's symptoms began with sore throat, cough and fever up to 100.5° F. The condition was diagnosed as "streptococcal tonsillitis" and he was treated with penicillin. Marked subjective improvement followed, but the temperature remained elevated and three days before admission, the patient again consulted a physician who told him his tonsils were still acutely inflamed. A blood

* This patient was studied and treated through the courtesy of Dr. Milton Sherry.

count at this time revealed leukocytosis of 50,000. The patient himself had noted slight cervical adenopathy during the three week period.

Past history, family history, and review of systems were essentially negative. The patient had spent two years in military service part of which was overseas, but had not been ill during that time. In the course of his professional work, the patient had frequently used roentgen-rays.

The significant physical findings on admission included elevation of temperature to 101.2° F.; a small conjunctival hemorrhage in the left eye; hypertrophied and infected tonsils; a few shotty posterior cervical lymph nodes and a single large lymph node in the left axilla. The lungs and heart were negative. The edge of the spleen was just palpable.

Admission blood picture showed a red cell count of 4.07 million; hemoglobin: 12.5 gm.; white blood cell count of 56,600 with 70 per cent monocytes, 1 per cent monoblasts, 12 per cent lymphocytes and 17 per cent segmented neutrophiles. The platelet count was 58,000. Bleeding and clotting times were normal. Serological test for syphilis was negative. Blood uric acid level was 6.1 mg. per cent. Other blood chemical tests were normal. Roentgen-ray of the chest was negative. Sternal marrow was examined on March 16, 1948 and revealed 71 per cent of the cells to be in the monocytic series with 15 per cent monoblasts. The remainder of the differential consisted of 19.5 per cent granulocytes, 1 per cent erythroid elements, and 8.5 per cent lymphocytes. A diagnosis of acute monocytic leukemia was made.

Course: The patient was hospitalized for a period of 20 days during which time he was treated with penicillin and received a single whole blood transfusion. No significant changes in the blood or bone marrow pictures were observed. After several weeks of rest he felt quite well subjectively, and attempted to resume his practice on a part-time basis. However, because of increasing fatigability and some dyspnea on exertion, he had to discontinue working and was readmitted to the hospital on May 3, 1948. The clinical and hematological findings were essentially unchanged. Admission blood study at this time revealed: Red blood cells 2.36 million; hemoglobin: 8 gm.; white blood cells: 51,000; platelets: 110,000. There were 80 per cent monocytes; 11 per cent granulocytes on differential white cell count.

Aminopterin mg. 1.0 per day was started on May 6, 1948, and continued for 15 days. During this interval the total white count fell from 51,000 to 4,450. The differential counts showed a steady decrease in monocytes to 25 per cent and a coincidental rise in granulocytes to 24 per cent, as well as an increase in mature lymphocytes to 30 to 50 per cent. The red cell count remained at a low level and the platelets likewise failed to show any increase. Bone marrow examinations on May 15 and May 19 showed a slight decrease in monocytes but persistence of monoblasts. The patient felt considerably better clinically. Aminopterin was discontinued on May 24, 1948, when the total white count fell below 4,000 and the patient was given 5 units of liver extract and 2 whole blood transfusions of 500 c.c. During the next seven days the white count rose gradually to 34,800 with an increased proportion of monocytes and monoblasts. From May 31 to June 4, the patient received 1.5 mg. of aminopterin every other day. From June 4 to June 12, he received 2.0 mg. of aminopterin daily. Only minor changes were noted in the peripheral blood and the bone marrow continued to show numerous monoblasts. Because of his subjective improvement, the patient was again discharged from the hospital on June 12. He had received a total of 43 mg. of aminopterin, numerous transfusions and, for a short period of time, concentrated liver extract.

Aminopterin mg. 2.0 per day was continued for three days after discharge but had to be discontinued when he quite suddenly developed a severe ulcerative stomatitis. He was then given folic acid, 20 mg. per day. The stomatitis improved but there was a coincidental rise in white count. By June 25, the total white count had risen to

278,000, with 66 per cent monoblasts in the peripheral blood. He was readmitted to the hospital on June 25 and died on June 27. The terminal picture was one of acute cardiac failure with marked pulmonary edema. A total dose of 50 mg. of aminopterin had been administered over a period of approximately six weeks. Permission for autopsy was granted.

The viscera displayed changes characteristic of acute monocytic leukemia. No changes indicative of drug effect could be seen on careful histological examination. An unexpected finding, however, was subacute appendicitis with perforation and a peri-appendiceal abscess. There had been no clinical indication of this lesion.

Comment: From May 6 to June 12, this patient with acute monocytic leukemia received a total dose of 49 mg. of aminopterin. During much of this time he felt quite well subjectively. Although there were marked alterations in the total leukocyte count, no significant or sustained improvement in the differential count or bone marrow picture occurred. The sudden occurrence of severe ulcerative stomatitis led to discontinuance of the drug and the temporary institution of folic acid therapy. This was promptly associated with a definite increase in the total leukocyte count which reached the highest point observed during the entire three month period of observation. It may be stated in summary, that at no time during the course of treatment was there any significant improvement in the hematological picture. The total duration of illness was approximately five months.

Case 6. B. P.,* a 15 yr. old white male student, was admitted on May 19, 1948. He had been in good health until five weeks prior to admission when he began to complain of fatigability and listlessness. Low grade fever developed which later rose to 101 to 102° F. He was thought to have a grippal infection and was treated at home by bed rest, expectorants and sedation. Since no improvement occurred, he was placed on salicylate therapy and after two weeks felt sufficiently well to return to school for two days. Recurrence of the fever and increasing pallor led the family doctor to advise hospitalization. The remainder of the history was non-contributory.

Admission physical examination revealed a well developed, somewhat obese white male who appeared acutely ill. There was marked pallor of the skin and mucous membranes. A small ecchymotic area, 2 cm. in diameter, was observed in the region of the right breast. Definite, but moderate, lymphadenopathy was present in the cervical, axillary and inguinal regions. The spleen could be felt three fingers'-breadth below the left costal border in the mid-clavicular line. The liver was not palpable. The remainder of the physical examination was essentially negative.

Admission laboratory studies revealed: Red blood cells: 2.26 million; hemoglobin: 6.1 gm.; white blood cells: 5,450; platelets: 86,000. The differential count demonstrated 3 per cent lymphoblasts, 95 per cent lymphocytes in varying stages of maturity, and 2 per cent granulocytes. Serological test for syphilis was negative. Blood chemical studies were within normal limits. Sternal marrow puncture revealed an extremely hypercellular marrow with the following differential: 14.5 per cent lymphoblasts, 79 per cent lymphocytes, of which only 11 per cent were mature forms, 2 per cent granulocytes and 4.5 per cent erythroid elements. A diagnosis of acute lymphoid leukemia was made.

Course: Aminopterin mg. 1.0 per day was begun on May 21, 1948. After six days the dose was increased to 1.5 mg. for a period of five days. No toxicity to the drug was evident nor were there any significant hematological changes, therefore, the

* This patient was studied through the courtesy of Dr. Willard Applefeld.

dosage of aminopterin was increased to 2.0 mg. daily. By June 15, the proportion of blasts in the peripheral blood had decreased somewhat and there was a slight increase in granulocytes up to 17 per cent. The white count which had averaged 5,500 dropped to 1,250, but the platelet count was maintained at approximately 150,000. A total dosage of 39 mg. of aminopterin had been administered up to June 15.

In spite of the lack of hematological change, the patient showed marked subjective improvement with increase in appetite and absence of discomfort. The temperature during the first two weeks of hospitalization fluctuated somewhat, but gradually fell to the point where there was only a low grade afternoon rise to 99 to 100° F. The red blood cell counts never rose above 3.77 million and were usually below 3.50 million in spite of numerous transfusions. A total of 19 transfusions of 500 c.c. each were given during the entire course.

On June 11, five units of concentrated liver extract per day was started concurrently with the aminopterin. Late in June, the patient experienced a transitory episode of gastrointestinal upset, associated with some diarrhea which was easily controlled. It was believed that this was a mild reaction to aminopterin but the drug was not discontinued. Slight stomatitis developed at the end of the month.

On July 1, 1948, the patient suddenly had a shaking chill followed by marked elevation of temperature. This was soon followed by nausea, vomiting and a severe watery diarrhea. Aminopterin was discontinued and folic acid in doses of 45 mg. per day was begun. The leukocyte count dropped to 600. Marked increase in the gastrointestinal symptoms was noted. The patient became definitely icteric and developed a diffuse eruption resembling an exfoliative dermatitis. He died on July 5, 1948 after an illness of approximately four months. Permission for autopsy could not be obtained.

Comment: Between May 19 and July 5, 1948 this patient with acute lymphoid leukemia received 71 mg. of aminopterin. For a portion of this time he also received five units of liver extract intramuscularly per day. Frequent blood transfusions were given and antibiotic therapy was liberally employed. During the first four weeks of his hospital course, the patient appeared clinically improved, but no significant hematological response was noted. Quite abruptly the patient developed signs of drug toxicity consisting of stomatitis and severe diarrhea. A feature of the clinical picture not previously observed in patients under aminopterin therapy was the development of a diffuse erythematous eruption which progressed almost to the point of exfoliation. The etiology of the terminal jaundice was somewhat obscure. In view of the liberal use of transfusions, the possibility of homologous serum jaundice cannot be dismissed.

Case 7. C. B.,* a 31 year old white, married female, housewife, was admitted to the hospital on June 30, 1948, complaining of weakness, malaise, and various hemorrhagic manifestations. In February 1948, she had become pregnant, but soon thereafter began to have slight uterine bleeding. Intensive estrogen therapy was given in an effort to arrest an impending abortion, but in spite of this the patient aborted. Therapeutic dilatation and curettage was necessary, subsequently, to control the bleeding. Four weeks following the operation, the patient developed what was thought to be "virus pneumonia" and at that time leukopenia, anemia and cervical glandular enlargement were noted for the first time. Penicillin therapy was given for this illness but subjective feelings of malaise and weakness persisted. The menstrual period in early June was unusually profuse. Because of the existence of marked

* This patient was studied through the courtesy of Dr. Joseph B. Gross.

anemia the patient was admitted to the hospital for study and treatment. Review of the systems yielded no additional significant information. The past history revealed several spontaneous abortions one of which in 1947, had also required subsequent dilatation and curettage.

The significant observations on physical examination on admission were: numerous purpuric spots scattered over the extremities and buttocks; slight enlargement of the cervical lymph nodes; very slight splenomegaly and hepatomegaly. A marked normocytic anemia was present as well as leukopenia with relative lymphocytosis. The platelets were reduced in number. Examination of the bone marrow revealed hypocellularity with an increase in lymphocytes. The picture at this time was suggestive of aplastic anemia rather than leukemia. A possible etiological association with estrogen therapy was considered. On discharge, July 14, 1948, the red count and hemoglobin were within normal limits as a result of transfusions, but the leukocytes, although normal in number, showed an abnormal differential characterized by an increase in mature lymphocytes.

During the next several weeks, the patient continued to complain of malaise and fatigability. Soreness of the mouth and gums appeared. With the onset of the next menstrual period profuse bleeding again occurred. Periodic observation of the peripheral blood demonstrated a steady rise in the total white count as well as the appearance of an increasing number of myelocytes and promyelocytes. Bone marrow examination at this time displayed a marked change from the previous observation. Hypercellularity was presented and 45 per cent of the cells were myeloblasts. A diagnosis of acute myeloid leukemia was made and the patient readmitted to the hospital on July 27, 1948.

The physical examination was essentially unchanged with the exception of new findings in the buccal cavity. The gums were hypertrophied, red and very tender. Laboratory studies on this admission revealed: Red blood cells: 2.57 million; hemoglobin: 7.3 gm.; white blood cells: 22,750; platelets: 230,000. Differential count showed 18 per cent granulocytes, 20 per cent lymphocytes, 18 per cent myelocytes, 32 per cent promyelocytes, and 12 per cent myeloblasts. Blood chemical studies were within normal limits. Other examinations likewise were negative.

Course: From July 27 to August 8, palliative therapy consisting of transfusions, penicillin, and local therapy to the gums was employed. Progressive rise in the white count, with increasing immaturity of the cells was observed. On August 8, 1948, aminopterin mg. 1.0 per day was started and continued for nine days when it was increased to 1.5 mg. per day. After approximately three weeks of this regime, the only significant change noted in the blood picture was an increased maturity of the cells of the granulocytic series. The predominant cell type at this time was the neutrophilic myelocyte of the "C" type. Hypertrophy of the gums, a problem before aminopterin therapy, increased in severity and was associated with ulceration and necrosis.

After a total of 28.5 mg. of aminopterin had been administered, the patient developed severe diarrhea characterized by the passage of 10 to 20 watery stools per day for about three days. During this period aminopterin was discontinued and folic acid mg. 15.0 per day was given. A coincidental rise in white cell count from 63,750 to 114,750 was observed. On September 4, the diarrhea having subsided, a-methopterin mg. 2.0 per day was begun. This was continued for 11 days, but no significant hematological changes were observed. Toward the end of this period, the total white count had risen to 199,250 and the proportion of 'blasts in the peripheral blood smears was increased. Aminopterin, mg. 1.5 per day was resumed on September 15 and continued thereafter.

Since no significant changes were noted in either the peripheral blood or bone marrow, urethane, gm. 3.0 per day, was begun on September 24 and given concur-

rently with the aminopterin. During the next two weeks, the patient became progressively worse clinically. The picture was characterized by increasing splenomegaly, marked abdominal distention, increasing severity of the lesions of the gums and the onset of icterus. Death occurred on October 7, 1948. The patient had received a total of 60.5 mg. of aminopterin, 22 mg. of a-methopterin and 42 gm. of urethane, over a period of two months. Permission for autopsy was not obtained.

Comment: Several clinical features are of interest in this case. The history of intensive estrogen therapy just prior to the onset of the hematologic disturbances is noteworthy but its significance can hardly be evaluated. The initial appearance of a hematological picture resembling aplastic anemia followed shortly thereafter by a typical leukemic state is likewise of interest. The use of several folic acid antagonists was without significant effect upon the clinical or hematological picture. The total duration of illness was approximately five and one-half months.

Case 8. L. R.,* a 63 year old white female, was admitted to the hospital on August 13, 1948. She had been in good health until six weeks before when she developed a perirectal abscess. This was treated successfully by incision and the patient felt well for two weeks. She then developed fever associated with sore throat, and right otitis media and was treated with penicillin. She improved again and blood count done at that time was said to have revealed no abnormalities. However, she never quite regained her strength and continued to have a slight afternoon elevation of temperature. She became progressively weaker and began to complain of "dizzy spells." Intermittent pain in the shoulders, arms and legs was also present. Approximately a week prior to admission she again developed sore throat and a slight cough and was again started on penicillin therapy. A repeat blood count on August 8 revealed 62,000 white blood cells with many blast forms. Hospitalization was advised for further study. History by systems and past history were essentially negative, except for an operation for uterine fibroids in 1927.

Admission physical examination revealed a well developed, somewhat obese white female who appeared acutely ill. The pharynx was injected and the tonsils were hypertrophied and markedly reddened. There were small shotty slightly tender lymph nodes in the anterior cervical chains. No other superficial lymphadenopathy was present. The chest was negative except for a few scattered basilar rales and rhonchi. Examination of the heart showed no abnormalities. The breasts were pendulous but normal. The abdomen was obese. No viscera or masses could be felt. There was tenderness on pressure over the long bones, but no peripheral edema or joint swelling. The remainder of the physical examination was essentially negative.

Laboratory studies on admission revealed: Red blood cells: 3.17 million; hemoglobin: 9.1 gm.; white blood cells: 158,500; and platelets, 300,000. Differential count: 26 per cent monoblasts, 57 per cent promonocytes, 13 per cent monocytes, 2 per cent lymphocytes and 2 per cent granulocytes. Serological test for syphilis was negative and all blood chemical studies were within normal limits with the exception of the uric acid level which was 5.7 mg. per cent. Bone marrow studies were not done because of the patient's extreme apprehensiveness. A diagnosis of acute monocytic leukemia was made.

Course: Aminopterin 1.0 mg. daily was begun on August 14, 1948. Four days after admission, the patient developed the physical signs of a bronchopneumonia at the left base, which was confirmed by roentgen-ray examination. The clinical picture was characterized by increasing dyspnea and cyanosis. Oxygen therapy was begun at

* This patient was studied through the courtesy of Dr. Richard Weinberger.

this time. On August 21, after having received 8 mg. of aminopterin, the patient developed diarrhea characterized by the passage of 10 to 12 watery stools per day. Slight stomatitis developed and a few ulcerated areas were noted in the pharynx. Aminopterin was reduced to 0.5 mg. daily and the patient was simultaneously started on 20 mg. of folic acid daily. The diarrhea did not improve with these measures, and, as a matter of fact, became even worse. The stools were observed to be blood tinged. The stomatitis and ulceration of the pharynx became more marked and some hypertrophy of the gums was likewise noted. The lesions in the pharynx which had begun as slightly elevated, reddened nodules, later became ulcerated and were covered with a gray-white necrotic membrane.

Aminopterin was discontinued on August 25, at which time folic acid was increased to 45 mg. daily, intramuscularly. In spite of all therapeutic efforts, bloody diarrhea persisted and the pulmonary pathology increased in severity. She could take no nourishment because of the ulceration in the pharynx. The patient died on August 27 after having become progressively more cyanotic and dyspneic.

During the 14 day period of observation and treatment, the white count varied between 163,500 and 42,000. There were no significant changes in the differential counts, the monoblasts averaging about 35 per cent and the promonocytes 49 per cent. It is interesting to note that thrombocytopenia was never present. Blood count on the day of death was: Red blood cells: 4.00 million; hemoglobin: 11.9 gm.; white blood cells: 99,250; platelets: 400,000. Differential: monoblasts 34 per cent; promonocytes 48 per cent; monocytes 10 per cent; lymphocytes 5 per cent, and granulocytes 3 per cent. The patient received a total dose of 10 mg. of aminopterin over a two week period.

An autopsy was performed. The pathological findings consisted for the most part of typical visceral infiltration with leukemic cells. Marked reticulo-endothelial hyperplasia was noted in the spleen and bone marrow. An interesting finding was the presence of numerous ulcerations throughout the esophagus, and small and large intestines. On histological examination these were found to coincide with focal areas of leukemic infiltration.

Comment: The duration of illness in this case of acute monocytic leukemia was approximately eight weeks. Evidences of drug toxicity appeared after only 8 mg. of aminopterin had been administered. The effort to combat these developments by the administration of folic acid may have been, in the light of subsequent concepts, actually detrimental to the patient. It is questionable, in view of the histopathology, whether one can attribute the extensive gastrointestinal ulcerations entirely to drug toxicity. At no time during the two week period of treatment was there evidence of clinical or hematological improvement.

Case 9. J. O.,* a 3 year old white female, was admitted to the hospital on August 9, 1948. She had been in good health until June 2, 1948, when she developed a swelling in the region of the left parotid gland, which extended somewhat down the neck. Shortly thereafter she developed pain in the left ear which soon began to drain a purulent material. Approximately five days later, swelling appeared on the right side of the neck, and also in the right temporal region and about the right eye. Within several days, facial paralysis was noted on the right and the patient was admitted to the Maryland General Hospital. Here blood findings indicative of acute myeloid leukemia were discovered. For the next six weeks palliative therapy, consisting of frequent blood transfusions and penicillin, was administered. During this time the

* This patient was studied through the courtesy of Dr. Lawrence C. Post.

right temporal swelling increased and proptosis of both eyes became quite marked. The remainder of the history was non-contributory. She was transferred on August 9 to the University Hospital for further study and treatment.

Physical examination revealed a well developed undernourished white female three years of age, lying quietly in bed, in no apparent distress. The skin was dry and warm and there were numerous purpuric and ecchymotic areas over the body. There was a smooth, non-tender swelling approximately 3 cm. in length over the right temporal region and a similar swelling in the left temporal area (figure 4). The superficial veins of the forehead were prominent, and there was marked bilateral exophthalmos. Some ptosis of the right upper eye-lid was present but no other evidence of facial palsy. Several conjunctival hemorrhages were present bilaterally. The extraocular movements could not be adequately tested. Pupils were round, regular and equal and reacted to light and accommodation. The fundi showed numerous small hemorrhages. The left ear drum was perforated and there was a slight purulent discharge. The pharynx appeared slightly injected and the tonsils were enlarged. No petechiae were seen in the buccal cavity. A stony-hard non-tender mass approximately the size of a pecan was visible and palpable in the left parotid region. Slight lymphadenopathy was noted in the right cervical area. The heart and lungs were normal. The spleen and liver were both just palpable at the costal margins. Numerous petechiae and purpuric areas were observed on the extremities.

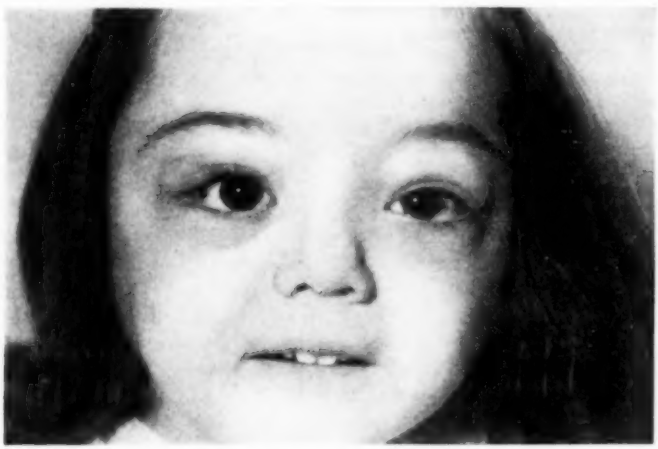


FIG. 4. Patient with acute myeloid leukemia (case 9). Note temporal and peri-orbital masses associated with bilateral proptosis.

Laboratory studies revealed: Red blood cells: 3.06 million; hemoglobin: 7.4 gm.: white blood cells: 35,500; platelets: 12,000. Differential count revealed: 4 per cent myeloblasts, 38 per cent promyelocytes, 16 per cent myelocytes "C," 16 per cent segmented neutrophiles and 28 per cent lymphocytes. Serological test for syphilis was negative. Blood chemical studies were within normal limits. Roentgen-rays of the skeleton were negative. Sternal bone marrow examination on August 13 showed 90 per cent of the cells to be in the granulocytic series, with 25 per cent myeloblasts and 36.5 per cent promyelocytes. There were 7 per cent lymphocytes and 3 per cent normoblasts. The marrow was exceedingly hyperplastic. A diagnosis of acute myeloid leukemia, with probable associated chloroma, was made.

Course: Supportive therapy, consisting of whole blood transfusions and penicillin, was started promptly. Aminopterin, 0.5 mg. daily, was begun on August 9. No significant changes occurred in the peripheral blood during the next four weeks. Leukocyte counts varied from 20 to 35,000. The platelets remained low. Red cell counts and hemoglobin were maintained at a level of 3.5 to 4 million by frequent transfusions.

The patient complained of generalized aches and pains in the back and extremities. Her appetite was poor at all times and she continued to run a febrile course. No change was noted in the size of the peri-orbital and temporal tumor masses. On August 30, after a dose of 10 mg. of aminopterin had been given a few small ulcerations appeared on the buccal mucous membranes. There was no diarrhea. The buccal ulceration cleared with local therapy, without discontinuation of the aminopterin. Approximately two weeks after the institution of aminopterin therapy, definite hirsutism was observed over the body. This was particularly noticeable on the posterior aspect of the chest, in the low back area and on the extremities. This finding persisted throughout her hospital stay.

Since no significant response was observed after a period of one month of aminopterin therapy, it was decided to switch to a-methopterin. This was begun on September 5 with a daily dose of 2.0 mg. and was continued for 10 days. No significant hematological or clinical response was observed during this time. The patient was discharged from the hospital on September 14, to continue on a similar regime under supervision of the family doctor. A-methopterin was continued during the succeeding 12 days at the end of which time profuse diarrhea began. A slight icteric tint was also noted. Severe anorexia and hyperpyrexia were present. The patient died on September 27, 1948. Permission for autopsy could not be obtained.

Comment: Over a period of 51 days this patient with acute myeloid leukemia received 13 mg. of aminopterin and 38 mg. of a-methopterin without any significant clinical or hematological response. The presence of superficial masses presumed to be composed of leukemic cells (chloroma), offered an additional objective for close observation. There was no decrease in the size of these tumor masses nor was any diminution of the proptosis visible. An interesting phenomenon observed in this case was the appearance of diffuse hirsutism over the body. Whether this represented a drug effect or was merely an evidence of the prolonged debilitating illness cannot be stated with assurance. The total duration of illness was approximately 4 months.

Case 10. H. B., an 11 month old white male infant, was admitted to the hospital on July 29, 1948. The history obtained from the parents indicated that the child had been ill since the latter part of June. The illness was characterized by signs of an acute respiratory infection associated with high fever. For this infection the patient was treated with sulfadiazine for a short time. The drug was soon discontinued because of the occurrence of vomiting. During the following weeks the child remained febrile, and anorexia and weight loss became marked. Increasing pallor and dyspnea were also noted. In the latter part of July "swellings" appeared on both sides of the neck. Hospitalization was advised by the family physician. The past history revealed an attack of whooping cough in January, 1948 and chickenpox in March, 1948. The remainder of the history was essentially negative.

Physical examination revealed a well developed but poorly nourished white male infant, breathing with some difficulty and with a distinct stridor. There was marked pallor of the skin and mucous membranes as well as a slight icteric tint. Petechiae were noted on the abdomen. The eyelids were puffy. Marked bilateral anterior and posterior cervical lymphadenopathy was present. Some lymph nodes measured up

to 2 cm. in diameter. There was a respiratory lag on the right side of the chest and dullness on percussion over this area. Auscultation revealed diminished breath sounds over the right hemithorax. The left lung was clear. Bilateral axillary lymphadenopathy was present. The heart appeared to be slightly enlarged or shifted to the left. Auscultation revealed a blowing systolic murmur over the entire precordium. The liver and spleen were both enlarged three fingers'-breadth below the costal margins. The extremities showed no abnormalities.

Blood study on admission revealed the following: Red blood cells 2.15 million; hemoglobin: 5.6 gm.; white blood cells: 117,200; platelets: 10,750. Differential count demonstrated 30 per cent lymphoblasts, 30 per cent young lymphocytes and 40 per cent mature lymphocytes. All other laboratory data were within normal limits. Roentgen-ray of the chest revealed a mass of enlarged glands in the superior mediastinum and a considerable amount of infiltration throughout the right lung. Roentgen-rays of the long bones were said to show periosteal changes compatible with acute leukemia.

For three days after admission to the hospital the patient's course was marked by continued fever. The temperature then fell to normal and continued so until August 12. At this time fever appeared again and was associated with obvious dyspnea. The liver and spleen became progressively larger. In spite of frequent transfusions, severe anemia persisted. Various hemorrhagic phenomena were present. On August 17, the twenty-first day of hospitalization, with the patient definitely appearing moribund, aminopterin, mg. 0.5 daily, was begun. At this time the peripheral blood picture was as follows: Red blood cells: 1.94 million; hemoglobin: 6.4 gm.; white blood cells: 30,000 and platelets: 3,800. Differential: 23 per cent lymphoblasts, 26 per cent young lymphocytes, 46 per cent mature lymphocytes and 5 per cent granulocytes. Tibial bone marrow examination on the same day revealed 96 per cent of the cells to be in the lymphoid series. There were 74 per cent lymphoblasts, 17 per cent young lymphocytes, 5 per cent mature lymphocytes and 4 per cent normoblasts. No granulocytic elements were seen. The marrow was exceedingly hyperplastic.

Aminopterin was continued for 12 days. During this time, the leukocyte count fell progressively from 42,000 to 7,200. The only significant change in the differential count noted during this time was an increase in granulocytes up to 25 per cent. After a total of 5.0 mg. of aminopterin had been given, rather profuse bleeding from the gums occurred and several small ulcerations appeared on the buccal mucous membranes. Jaundice, which had been present to a mild degree, became more marked. A pathological fracture of the right humerus was noted on August 26. On August 29, 1948, the patient suddenly became intensely cyanotic and dyspneic, and died. Permission for autopsy was obtained. The significant findings were marked lymphoid hyperplasia, which was particularly pronounced in the thymus; and diffuse hemorrhages throughout the viscera. Extensive subdural and subarachnoid hemorrhages were present. Histopathological study demonstrated leukemic infiltration of the viscera.

Comment: This infant with acute lymphoid leukemia was moribund at the time aminopterin therapy was begun. In all, the patient received a total of 6 mg. of the drug with no remarkable clinical or hematological response. Ulcerative stomatitis appeared after 3 mg. of aminopterin. Death was probably hastened by an uncontrollable hemorrhagic diathesis.

Case 11. D. B., a 22 month old white female infant, was admitted to the hospital on February 12, 1949. She had been in good health until six days before admission when an acute respiratory infection developed. Three days later petechiae were observed on the trunk and extremities and marked pallor was noted. The patient was seen by the family physician and hospitalization was advised. Past history revealed

that the patient had had mumps in January 1948, chickenpox in March 1948 and measles in December 1948. Review of systems was essentially negative.

Physical examination revealed a well developed, well nourished white female with marked pallor of the skin and mucous membranes. Numerous petechiae were noted on the trunk and extremities. Large ecchymotic areas were also present on the forehead and over the lower abdominal wall. There was dullness to percussion over both lower lung fields and a few crepitant râles were heard in these areas. The abdomen was moderately distended. The liver was palpable four fingers'-breadth below the costal margin. The spleen was easily palpable three fingers'-breadth below the costal margin. Slight generalized lymphadenopathy was present. The remainder of the physical examination was essentially negative.

Admission laboratory studies revealed: Red blood cells: 2.87 million; hemoglobin: 4.2 gm.; white blood cells: 34,400; and platelets: 16,800. Differential: lymphoblasts 5 per cent, young lymphocytes 4 per cent and mature lymphocytes 91 per cent. Routine urine examination was negative. Serological test for syphilis was negative. All blood chemical studies were within normal limits. Bone marrow examination revealed 46.5 per cent lymphoblasts, 19.5 per cent young lymphocytes, 28.0 per cent mature lymphocytes, 1.5 per cent neutrophilic metamyelocytes, 2 per cent segmented neutrophiles and 2.5 per cent erythroid elements. A diagnosis of acute lymphatic leukemia was made.

Course: The patient was given supportive therapy consisting of transfusions and antibiotics for several days after admission. Aminopterin 0.5 mg. per day was begun on February 15. In spite of therapy daily spikes of temperature to 103° to 104° F. continued unabated. Soon the patient began to exhibit severe hemorrhagic manifestations. These consisted of repeated epistaxes, hematemesis and showers of petechiae over the extremities. In an effort to control the bleeding tendency, toluidine blue, 3.0 mg./kg. intravenously in physiological saline solution, was given on several consecutive days but without apparent effect. In spite of all efforts, the course was rapidly downward and the patient died on February 23. A blood count on that day revealed the following: Red blood cells: 2.21 million; hemoglobin: 5.9 gm.; white blood cells: 3,200 and platelets: 6,600. Differential revealed: lymphoblasts 12 per cent, young lymphocytes 10 per cent, mature lymphocytes 76 per cent, and segmented neutrophiles 2 per cent. Permission for autopsy was obtained. The postmortem examination revealed typical findings of an acute leukemia. No changes attributable to aminopterin therapy were observed.

Comment: The total duration of illness in this case of acute lymphoid leukemia was approximately three weeks. The administration of 4.5 mg. of aminopterin over a period of nine days produced no clinical or hematological changes. Death appeared to be due to an overwhelming hemorrhagic diathesis. This occurred so soon after the initiation of aminopterin therapy that it is difficult to relate it to the administration of the drug.

Case 12. G. N.,* a 60 year old white male automobile mechanic, was admitted to the hospital on April 2, 1949. The patient had been in good health until one month before admission when he developed an acute respiratory infection and began to experience slight precordial chest pain. Penicillin and sulfadiazine were given by his family physician for several weeks without significant improvement. Hospitalization was advised. Past history revealed that the patient had had considerable difficulty over many years with infected, thrombotic internal and external hemorrhoids. Review of systems was essentially negative.

Physical examination revealed a well developed, somewhat obese white male.

* This patient was studied through the courtesy of Dr. Loy Zimmerman.

There was pallor of the skin and mucous membranes. Slight generalized lymphadenopathy was present. There was dullness on percussion over the right upper and middle lung fields and crepitant râles and rhonchi were heard in these areas. The liver was palpable three fingers'-breadth below the costal margin. The edge of the spleen was palpable at the costal margin. An anal stricture was present and several large infected and thrombotic external hemorrhoids were observed. The remainder of the physical examination was essentially negative.

Admission laboratory studies revealed: Red blood cells: 2.66 million; hemoglobin: 7.2 gm.; white blood cells: 8,500; and platelets: 137,640. Differential: monoblasts 10 per cent, promonocytes 12 per cent, monocytes 18 per cent, mature lymphocytes 48 per cent and segmented neutrophiles 12 per cent. Routine urinalysis was negative. Serological test for syphilis was negative. All blood chemical studies were within normal limits. Roentgen-rays of the chest revealed a bilateral basilar pneumonitis. Bone marrow examination on February 12 revealed: 19 per cent monoblasts, 14.5 per cent promonocytes, 14 per cent monocytes, 2 per cent lymphocytes, 3 per cent plasma cells, 2 per cent myeloblasts, 11.5 per cent myelocytes, 11 per cent neutrophilic metamyelocytes, 8.0 per cent segmented neutrophiles and 15 per cent erythroid elements. The marrow was quite hypercellular. A diagnosis of acute monocytic leukemia was made.

Course: For the first three weeks of his hospital stay the patient was treated in a symptomatic manner. He received a number of transfusions and large doses of penicillin. In spite of this regime daily temperature elevations continued. The thrombotic, infected hemorrhoids were a source of constant discomfort. No significant hematological changes occurred. Aminopterin, 1.0 mg. per day, was begun on April 23, 1949. At this time, also, aureomycin, 250 mg. every four hours, was started. At the end of approximately a week significant changes became apparent in the peripheral blood. There was a gradually increasing proportion of mature granulocytes and corresponding reduction in the immature monocytes. A typical blood picture is that of May 11: Red blood cells: 4.0 million; hemoglobin: 11.6 gm.; white blood cells 2800; platelets: 256,000. The differential count revealed the following: polymorphonuclears 54 per cent; neutrophilic metamyelocytes 29 per cent; lymphocytes 16 per cent; monocytes 1 per cent.

In spite of the striking improvement in the peripheral blood picture, the patient continued to run a febrile course. The hemorrhoids became necrotic and gangrenous and evidences of severe proctitis were present. On May 14 an icteric tint was noted in the sclerae. During the next several days, jaundice became more profound and the patient gradually lapsed into a stuporous state. Death occurred on May 17. Permission for autopsy could not be obtained.

Comment: This patient with acute monocytic leukemia lived for approximately two and one-half months after the onset of symptoms. In the last three weeks of his illness he received 20 mg. of aminopterin and during this time showed marked improvement in the peripheral blood picture. He remained febrile, however, and developed severe proctitis and gangrene of thrombotic hemorrhoids. The terminal picture was dominated by a rapidly progressive jaundice. Since no autopsy could be obtained, the pathological basis of the icterus remains obscure. This patient as well as several others in the series with a similar picture of terminal icterus had received large quantities of blood. The possibility of homologous serum jaundice and/or drug toxicity must be considered as etiological factors.

Case 13. M. K.,* a 26 year old white male dentist, was admitted to the hospital on April 20, 1949. He had been in good health until eight days before admission when he developed an acute respiratory infection. This was followed by headache, malaise and fatigability. At the same time, he began to experience tenderness and pain in the gums. A colleague whom he consulted suggested thorough physical examination and laboratory studies. A blood study was made following which hospitalization was advised. The past history and review of systems failed to add other contributory information.

Physical examination revealed a well developed nourished white male. There was marked pallor of the skin and mucous membranes. Slight hypertrophy of the upper gums on the left was present. Several petechiae were observed on the buccal mucous membranes. Remainder of the physical examination was essentially negative.

Admission laboratory studies revealed: White blood cells: 60,150; red blood cells: 2.86 million; hemoglobin: 7.3 grams; platelets: 14,400. Differential: lymphoblasts 86 per cent, young lymphocytes 2 per cent, mature lymphocytes 9 per cent and segmented neutrophiles 3 per cent. Routine urine examination was negative. Serologic test for syphilis was negative. All blood chemical studies were within normal limits. Bone marrow examination revealed: 81.5 per cent lymphoblasts, 9.0 per cent young lymphocytes, 5.0 per cent mature lymphocytes, 4.0 per cent neutrophilic metamyelocytes and 0.5 per cent erythroid elements. The marrow was exceedingly hypercellular. A diagnosis of acute lymphoid leukemia was made.

Course: After receiving several transfusions, the patient was started on aminopterin, mg. 1.0 per day, on April 23. Aureomycin, 1.5 gm. daily, was likewise administered. After approximately one week of this régime, there was definite clinical improvement. Fever which had been present during the first several days of his hospital stay, subsided. However, no significant hematological changes occurred. Because of continuance of the state of clinical well-being, the patient was discharged from the hospital on May 11, and provisions were made to continue the same therapy on an out-patient basis. Blood study on the day of discharge revealed the following: Red blood cells: 4.0 million; hemoglobin: 12.0 gm.; white blood cells: 98,000; platelets: 480,000. The differential count revealed 93 per cent lymphoblasts, 5 per cent mature lymphocytes and 2 per cent monocytes.

After several days at home the patient again began to experience malaise and developed an afternoon elevation of temperature. He was readmitted to the hospital on May 17. The blood picture was unchanged. At this time physical signs of pneumonitis at the base of the right lung were found. During the next six days, temperature persisted at a constant level of 103° to 104° F.

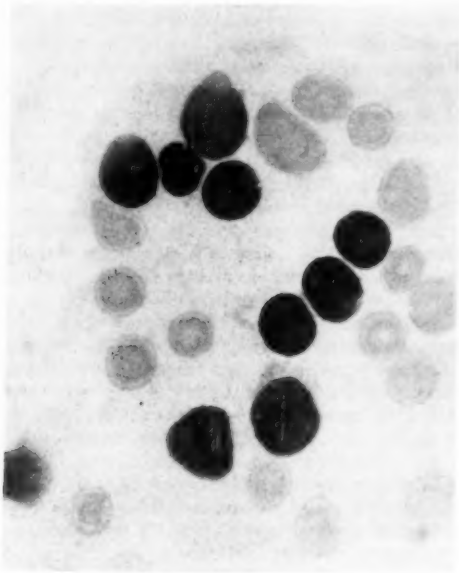
Evidence of extension of the pneumonic process was observed. In spite of continuance of large doses of penicillin and aureomycin, the patient died on May 23. Permission for autopsy could not be obtained.

Comment: The total duration of illness in this patient was approximately six weeks. During four weeks of this time he received a total of 27 mg. of aminopterin in daily doses of 1.0 mg. each. For approximately three weeks, while on a regime of frequent blood transfusions, aureomycin and aminopterin, the patient experienced a definite clinical remission characterized by absence of temperature, increase in strength and appetite as well as improvement of the oral lesions. At no time, however, was there any change in the blood picture. The terminal period was characterized by a pneumonic

* This patient was studied through the courtesy of Dr. Louis E. Wice.

process of sudden onset and rapid course. The administration of large doses of antibiotics apparently had no effect upon the pulmonary pathology.

Case 14. C. H.,* a 14 month old white male, was admitted to the hospital on April 12, 1949. He had been in good health until 10 days before admission when his mother noted abdominal enlargement, anorexia, cough and slight dyspnea. Shortly thereafter an acute respiratory infection developed. He was seen by the family physician who made a diagnosis of pneumonia and started treatment with sulfadiazine. Several days later marked pallor was noted and petechiae were observed on the trunk and extremities. Hospitalization was advised. Past history and review of systems were essentially negative.



(a)

FIG. 5.

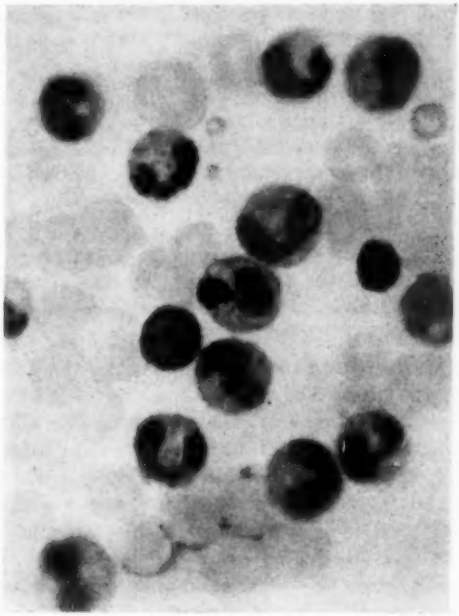
Physical examination revealed a well developed, well nourished white male child. There was marked pallor of the skin and mucous membranes. Moderate generalized lymphadenopathy was noted. The liver and spleen were both palpable three fingers'-breadth below the costal margin. A number of petechiae were observed on the trunk and extremities. The remainder of the physical examination was essentially negative.

Admission laboratory studies revealed: Red blood cells: 910,000; hemoglobin: 3.0 grams; white blood cells: 33,550, and platelets: 6,800. Differential: lymphoblasts 20 per cent, young lymphocytes 9 per cent, mature lymphocytes 57 per cent, segmented neutrophiles 11 per cent; basophiles 1 per cent and myelocytes C 2 per cent. Routine urine examination was negative. Blood uric acid 9.2 mg. per cent, bilirubin—direct 0.5 mg. per cent, indirect 1.3 mg. per cent; albumin 3.30 gm. per cent; globulin 1.03 gm. per cent. Several heterophile antibody agglutination tests were reported as

* This patient was studied through the courtesy of Dr. William Seabold.

negative. Bone marrow examination on April 12, 1949 revealed an increase in cellularity. The differential count was as follows: lymphoblasts 81.0 per cent, young lymphocytes 5.0 per cent, mature lymphocytes 4.5 per cent, granulocytes 6.0 per cent, and erythroid elements 3.5 per cent (figure 5). A diagnosis of acute lymphoid leukemia was made.

Course: Supportive therapy, consisting of frequent blood transfusions and antibiotics, was promptly started. The antibiotic selected for use in this patient was aureomycin which was given orally in doses of 250 mg. every four hours. Aminopterin 0.5 mg. daily intramuscularly was started on April 14. There was slight clinical improvement during the next two weeks. Moderate reduction in the size of the liver,



(b)

FIG. 5. Bone marrow (case 14). Representative microscopic fields (× 1000) before treatment (a) and after treatment (b) with aminopterin. Note predominance of 'blasts in pretreatment marrow.

spleen and lymph nodes was observed. The red blood cell count and hemoglobin were maintained by frequent transfusions during this time. The leukocyte count gradually dropped, and lymphoblasts disappeared from the peripheral blood. On May 4, marked hemorrhagic manifestations appeared. The patient began to have frequent spontaneous epistaxes, hematemesis, and frequent loose bloody stools. Numerous petechiae and purpuric lesions were observed over the body. Aminopterin was discontinued on that day after a total dose of 10.5 mg. had been given. The diarrhea and hemorrhagic diathesis continued during the next three days. The temperature climbed steadily and the patient's condition appeared critical. In the midst of this critical period significant changes were observed in the peripheral blood. The differential count of

May 11 revealed: segmented neutrophiles 30 per cent, eosinophiles 2 per cent, basophiles 1 per cent, monocytes 1 per cent, mature lymphocytes 32 per cent, promyelocytes 17 per cent and myelocytes C 16 per cent. Platelet levels which had been as low as 3,500 were observed, in a period of a few days, to rise to 260,000.

Aminopterin, 0.5 mg. every other day, was resumed on May 11. Bone marrow examination on May 16, 1949 revealed a marked change when compared to the previous study of April 12. An increase in cellularity was present but the majority of cells at this time were of the myeloid series. The differential count was as follows: myeloblasts 0.75 per cent, promyelocytes 1.25 per cent, myelocytes C 13.5 per cent, neutrophilic metamyelocytes 57.75 per cent, segmented neutrophiles 12.0 per cent, mature lymphocytes 2.25 per cent, normoblastic erythroid elements 7.25 per cent, and megaloblastic erythroid elements 5.25 per cent. The picture represented a complete change from that of an acute lymphoblastic leukemia to one of marked myeloid hyperplasia. Evidences of distortion of erythroid maturation were present. Typical megaloblastic changes were observed in 5.25 per cent of the erythroid cells. A number of the polymorphonuclear neutrophiles were observed to have hypersegmented nuclei and "giant" metamyelocytes were also noted.

In the following two weeks marked clinical and hematological improvement continued. The liver and spleen were no longer palpable. The patient became afebrile and all evidences of a hemorrhagic tendency disappeared. Blood studies on May 20 revealed: Red blood cells: 5.16; hemoglobin: 12.8 gm.; white blood cells: 9,300 and platelets: 958,000. Differential: segmented neutrophiles 71 per cent; monocytes 3 per cent, mature lymphocytes 25 per cent and myelocytes C 1 per cent. The patient was discharged from the hospital on May 27 with a perfectly normal peripheral blood picture. All medication was discontinued with the exception of aminopterin which was continued in doses of 0.25 mg. per day orally.

Comment: This 14-month old child with acute lymphoid leukemia had been ill for approximately 12 days when the diagnosis was established and therapy begun. The therapeutic regime consisted of the liberal use of whole blood and aureomycin, 1.5 gm. per day, as well as aminopterin, 0.5 mg. per day. Although evidences of a hemorrhagic tendency had been present since admission, these became more marked after the patient had received 10.5 mg. of the folic acid antagonist. At a time when the patient appeared moribund, significant changes were observed in the peripheral blood. Blood studies during the following weeks showed an increasing trend toward normal. The platelets rose spontaneously and numerous immature cells of the myeloid series were seen in peripheral blood smears. Examination of the bone marrow showed complete disappearance of 'blasts, myeloid hyperplasia and changes in the erythroid cells and granulocytes characteristic of a deficiency of the E. M. F. For approximately one month (June, 1949) the patient has been in a complete clinical and hematological remission.

Discussion

Utilization of folic acid antagonists in the therapy of leukemia and other neoplastic diseases is based primarily upon the principle of the biological competition of structurally related compounds.[8] This concept has become a guiding factor of increasing importance in pharmacologic research since the publication of the Woods-Fildes[9] theory of the mode of action of sulfon-

amides in 1940. The synthesis of folic acid was achieved in 1946.[10] It has been found to consist of para-amino benzoic acid, glutamic acid and a pteridine ring. Knowledge of the basic structure of the vitamin afforded the opportunity for the synthesis of related structural analogues. The antifolic acid activity of these analogues was tested by their ability to inhibit the bacterial growth-promoting powers of the metabolite.[11] On this basis, the most potent analogue thus far synthesized has been aminopterin. Even though a number of related compounds have already been prepared, the potential number and variety of analogues is far from exhausted. The therapeutic usefulness of future compounds of this nature will require intensive investigation.

The mechanism of action of folic acid antagonists remains, as yet, largely unanswered. There is no definitive evidence that neutralization of the bacterial growth-promoting activity of the vitamin is necessarily indicative of the therapeutic potentialities of an anti-vitamin. Further studies of the effects of these antagonists upon animal and human metabolism remain to be accomplished. It may be worth while to review briefly some of the known metabolic effects of this vitamin in various bacterial and animal species.

Folic acid is an essential growth factor for many bacterial species.[12, 13, 14, 15] There is experimental evidence that the vitamin is of importance in nucleoprotein metabolism.[16, 17] Animal studies have demonstrated that folic acid deficiency is associated with marked anemia, granulocytopenia, and severe diarrhea leading ultimately to death.[18, 19, 20] It is possible, in rats, to produce a folic acid deficient state by the prolonged administration of sulfonamides to animals maintained on controlled diets.[21, 22] This effect is probably due to the action of the chemotherapeutic agent upon intestinal microörganisms concerned normally with the synthesis of folic acid. Pathological examination of these animals revealed marked hypoplasia of the bone marrow. Administration of the vitamin resulted in reversal of these changes. The striking influence of folic acid upon the hematological abnormalities of various types of macrocytic anemia has been well-documented recently.[23] In spite of the wealth of experimental data accumulated thus far, however, many aspects of the physiological activity of folic acid are still quite obscure.

The relationship of folic acid and its analogues to neoplastic disease has become of interest during the past several years. In 1944 Williams [24, 25] reported that a study of the vitamin B complex content of various human and animal neoplasms revealed that these malignancies contained a higher concentration of folic acid than any normal tissue. Leuchtenberger et al.[26] in 1944 were the first to report that the administration of crude folic acid derivatives, "folic acid concentrate" and crystalline *L. casei* factor, inhibited the growth of a transplanted tumor, Sarcoma 180, in mice. Further studies by these workers [27] resulted in the report that the daily intravenous administration of 5 micrograms of fermentation *L. casei* factor resulted in the complete regression of spontaneous breast cancers in 38 of 89 mice. Other investigators [28, 29, 30] were unable to corroborate these results. The discovery

of the structure and synthesis of folic acid,[10] clarified this discrepancy. Fermentation *L. casei* factor was found to be a conjugate of folic acid containing three molecules of glutamic acid in contrast to the metabolite itself which contained only one molecule of this amino acid. Repetition of the experiments cited above by Lewisohn et al.,[31] with liver *L. casei* factor (pteroylglutamic acid), failed to reproduce the results previously obtained. The possibility that the folic acid conjugate, pteroyltriglutamic acid, might have been therapeutically active against experimental tumors because of its structural similarity to the vitamin, provided a stimulus for the synthesis and testing of other compounds structurally related to folic acid.

A number of recent investigations have indicated that 4-amino folic acid (aminopterin) and other analogues appear to have significant activity against various experimental tumors. Little et al.[32] observed that the administration of aminopterin to baby chicks resulted in the inhibition of growth of the Rous chicken sarcoma. Schoenbach et al.[33] reported that aminopterin retarded the growth of sarcoma 180 in mice and produced striking alterations in the histology of the tumor. Moore et al.[34] demonstrated growth inhibition of sarcoma 180 by another folic acid antagonist, 4 amino-N^{10} methyl pteroylglutamic acid (a-methopterin). Burchenal and associates[35] reported that aminopterin demonstrated only slight and irregular chemotherapeutic activity in prolonging the survival time of mice injected with transmitted leukemias, whereas a-methopterin caused as great or greater prolongation of the survival time as the nitrogen mustards. Higgins and Woods[36] have demonstrated that aminopterin restricted the growth of a transplanted spontaneous mammary tumor in mice, during the period that the drug was administered.

It is possible at this time to attempt only an interim evaluation of the influence of aminopterin upon acute leukemia in humans. Careful study of the pertinent literature, which has been previously cited, reveals a certain degree of unanimity concerning some aspects of this form of therapy. One may attempt to summarize these views. The folic acid antagonists so far available do not appear to be suitable for the therapy of chronic leukemia since the margin of safety between therapeutic and toxic effect is too slim to permit long-term treatment and since there already exist other forms of therapy which are at least temporarily beneficial.[37] The helplessness of the clinician confronted with acute leukemia is in striking contrast to this situation. There is general agreement, in spite of many failures, that the incidence of temporary clinical and hematological remissions observed in patients with acute leukemia treated with these agents far exceeds previous experience with spontaneous remissions and must, therefore, be causally related to the therapy. Review of the reported cases indicates that therapeutic benefits are more likely to occur in children than in older persons. By current methods of study, it has not been possible to predict the response of a given case of acute leukemia to these compounds. There has been some attempt to correlate the variety of leukemia with the therapeutic response. In general, leukemia of the lymphoblastic variety has responded somewhat

better than other types. Most investigators who have analyzed their data in terms of cell type agree on the apparent lack of response of acute monocytic leukemia. The response of myeloblastic leukemia is intermediate. Current methods of cytological study do not always permit absolute identification of cells at the 'blast level of differentiation. Hitherto, this limitation has been considered of more or less academic significance. Cell identification by more refined technics is distinctly needed for further progress in the management of this disease. In the largest group of cases reported so far, that of Farber,[2] results have been given in terms of the total group and no effort has been made to relate cell type to response. It has been noted, moreover, that only certain types of transmissible leukemias, even of the same cell type, appear to respond to aminopterin therapy. The use of another host for experimental investigation may result in an apparent lack of response when a type of leukemia which appeared to be sensitive was employed. The complexity of evaluating therapy in clinical leukemia, where the characterization of the leukemic process and the genetic constitution of the host are unknown, is evident.

Problems of dosage of folic acid antagonists have, in the recent past, been dealt with largely in an empirical fashion. Virtually no data exist regarding absorption, rate of excretion, and metabolism of the anti-folic acid compounds. It seems likely that a principle established in previous experiments with anti-vitamins is valid for the folic acid antagonists, i.e., the absolute amount administered is of less significance than the ratio established between the metabolite and anti-metabolite. Wooley has referred to this ratio as the inhibition index.[6] The induction of a folic acid deficient state in humans may be expected to be associated with some of the signs found in the experimental animal similarly affected. In a disease such as acute leukemia it is difficult at times to distinguish toxic manifestations from those due to the progression of the disease itself. Nevertheless, certain toxic effects could be differentiated. These will be discussed in more detail below. It has been customary hitherto to administer the drug intramuscularly although recent evidence indicates that it has been equally effective in some patients when given orally.[3] The doses employed have varied only slightly in individuals with considerable variation in body size. Thus in young children, the customary dose has been 0.5 to 1.0 mg. daily whereas in adults 1.0 to 2.0 mg. daily have been employed. Some patients in our series have been able to take relatively large doses before the occurrence of toxic effect while others have shown early signs of toxicity. The reasons for this variability cannot be stated with certainty although a possible explanation may lie in the vitamin-anti-vitamin ratio previously referred to. In those patients who have undergone partial or complete temporary remissions, maintenance therapy is considered advisable.

Among the toxic phenomena associated with the employment of folic acid antagonists may be listed the following: ulcerative stomatitis, diarrhea, bone marrow aplasia and alopecia. Certain other manifestations have also

been observed but their causal connection with the specific therapy is less well defined. In the latter category may be listed icterus, diffuse erythematous skin eruption, and an exaggerated hemorrhagic diathesis. The toxic complications mentioned in the first category are distinctly suggestive of folic acid-deficiency signs noted in experimental animals, particularly the so-called vitamin M deficiency described in monkeys.[18] The stomatitis and diarrhea are perhaps the earliest toxic signs to be noted. The former begins with scattered erythematous areas on the tongue and buccal mucous membranes which rapidly progress to central ulceration covered by a dirty gray-white membrane. The diarrhea is characterized by frequent watery stools which at times are distinctly bloody and are associated with marked tenesmus. Evaluation of the degree of bone marrow aplasia is somewhat difficult because of the underlying leukemic process. In general, one observes diminished cellularity and a predominance of small, mature lymphocytes in the marrow. The peripheral blood simultaneously reveals increasing leukopenia which again is often difficult to evaluate because of the well-known variations in leukocyte count observed even in untreated acute leukemia. Diffuse alopecia, a phenomenon of lesser importance, is regularly noted in patients who have been maintained for any length of time on the drug. This manifestation is clearly analogous to the skin disturbances noted in experimentally-induced folic acid deficiency in animals. Terminal icterus has been noted in several patients in our series. Because of the use of massive quantities of whole blood in these patients, the possibility of a viral etiology rather than drug toxicity cannot be entirely disregarded. Pathological study of the liver in these cases has not helped to clarify this problem. Many observers have noted an excessive hemorrhagic tendency in patients under aminopterin therapy. Again, because of the concomitant thrombopenia due to the leukemic process, evaluation of the influence of the drug in producing or accelerating the hemorrhagic diathesis is somewhat difficult. In view of the recent reports of Allen et al.[25] regarding the presence of a heparin-like material in the blood of patients with acute leukemia, therapeutic efforts have been made to control the hemorrhagic process by the intravenous administration of toluidine blue. Results have been equivocal. In general, current concepts regarding the management of toxic phenomena consist of either temporarily discontinuing the drug or continuing its use at a lower dosage level. The concomitant administration of liver extract has not noticeably alleviated the toxic effects. The use of folic acid, while theoretically correct, has not been encouraged because of possible intensification of the leukemic process.

It is obvious from this brief survey that the folic acid antagonists hitherto employed possess many disadvantages. The narrow margin between therapeutic efficacy and toxicity renders widespread and uncontrolled use of these compounds somewhat hazardous. The gaps in knowledge regarding many fundamental aspects of the use of these anti-vitamins have been pointed out. Nevertheless, the occurrence of undisputed remissions to an extent hitherto

unheard of in acute leukemia offers sufficient incentive to an even more intensive pursuit of this line of investigation.

Addendum: Since this manuscript was submitted for publication, case 14 experienced a relapse of his leukemic process two months later while still receiving aminopterin. Further therapy did not influence the course of the disease and he died soon thereafter.

Six additional cases have received aminopterin since June 1949. Two patients had acute lymphatic leukemia. One patient, aged 11 years, showed no evident response. The other, aged two and one-half years, experienced a complete hematological and clinical remission for a period of four months. Relapse occurred followed shortly thereafter by death. Two cases of acute monocytic leukemia, aged 22 and 56 years, respectively, showed no response. One case of leukosarcoma in a 32 year old male did not improve with aminopterin therapy. One patient, aged 35 years, with acute myelogenous leukemia demonstrated a partial hematological response although no evident clinical improvement occurred. Death was characterized by extensive hemorrhagic phenomena.

Summary

1. Detailed studies of 14 patients with acute leukemia treated with aminopterin and a-methopterin have been presented. Included in the group were six children, 11 months to eight years of age; two young adults, 15 and 17 years of age, respectively; and six adults, 26 to 63 years of age. There were four cases of acute myeloid leukemia, seven of the acute lymphoid variety, and three of the acute monocytic type.

2. The therapeutic regimen employed consisted of the liberal use of whole blood transfusions, various antibiotics, and the folic acid antagonists, aminopterin and a-methopterin. The former was given in doses of 0.5 to 2.0 mg. per day intramuscularly and the latter in doses of 2.0 to 4.0 mg. daily.

3. Responses to therapy were classified in the following groups: (a) Complete temporary clinical and hematological remission; (b) partial temporary remission; (c) no response. Criteria for these responses were presented.

4. Two patients, cases 1 and 14, were considered to have undergone complete temporary clinical and hematological remissions. The duration of remission in case 1 was 81 days following which relapse and death occurred. Case 14 has had complete remission for approximately 30 days (June, 1949).

5. Partial temporary remissions were observed in three patients all of whom subsequently died.

6. The course of the disease in nine patients was considered to have been uninfluenced by the therapy employed.

7. The rationale, toxic manifestations, and current concepts regarding the use of folic acid antagonists were discussed.

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TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA WITH LANATOSIDE C*

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Since an acute attack of paroxysmal auricular tachycardia may occasionally precipitate heart failure and even death if allowed to persist over long periods of time, it is desirable to terminate each attack as quickly as possible. The drug used should be non-toxic, rapid in its action, and certain in its effect. Unpleasant side effects are to be avoided if possible. Such drugs as quinidine and mecholyl which are commonly used in the treatment of this condition have the disadvantage of both unpleasant side effects and fairly frequent toxic manifestations, nor do they always stop the attack. It was because of these disadvantages that we tried intravenous rapid digitalization with Lanatoside C.

Method

Patients chosen for a trial of this drug were patients who had the clinical and electrocardiographic findings of paroxysmal supraventricular (auricular or nodal) tachycardia. They were also given a thorough trial of the more innocuous procedures such as carotid sinus and ocular pressure, gagging, and Valsalva maneuver before being given the drug. It was felt that a trial of less than five minutes with the above methods was insufficient since many cases can be reverted to normal by one of these measures.

With failure of vagus stimulation in 26 patients, Lanatoside C was given intravenously. A period of 60 to 120 seconds was used for the injection and a total of usually 1.2 mg. of the drug was used. This dose was chosen because it worked in the majority of cases and yet in no case did this dose produce nausea. (Nausea was the only unpleasant symptom produced by this drug in any of our patients.) If in 30 minutes the rhythm had not reverted to normal 0.4 mg. more was given in the vein. In one case (number 11) a third dose of 0.4 mg. was necessary before the rhythm was controlled, but in the remainder 1.2 to 1.6 sufficed. Usually before a second dose of Lanatoside C was given, carotid sinus and ocular pressure were tried again as digitalis seems to sensitize the vagus in many cases.

The pulse was checked at frequent intervals during the first 30 minutes and about every 10 minutes thereafter until the rhythm reverted to normal. Often the patient notified us that "my heart has quit running away." A second electrocardiogram was taken after the abnormal rhythm had ceased.

Results

The results are tabulated in table 1. A total of 26 cases did not respond to vagal stimulation and required Lanatoside C. The average age of the

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TABLE I

Case No.	Age	Sex	Previous Attacks	Other Diseases	Duration of Attack	Signs of Failure	Dose of Lanatoside C	Time for Conversion
1	18	M	No	None	5 hours	No	1.6 mg.	12 minutes
2	24	M	Yes	None	3 hours	No	1.6 mg.	18 minutes
3	23	M	Yes	Neurocirculatory asthenia	1 hour	No	1.6 mg.	21 minutes
4	72	M	Yes	A. S. heart disease	7 hours	Yes	1.2 mg.	28 minutes
5	26	F	Yes	None	5 hours	No	1.2 mg.	13 minutes
6	46	M	No	None	14 hours	No	1.2 mg.	4 minutes
7	55	F	No	Chronic cholecystitis	6 hours(?)	No	1.2 mg.	7 minutes
8	38	F	No	Pulmonary embolism	2 hours(?)	Yes	1.2 mg. 0.4 mg.	50 minutes
9	48	F	Yes	None	30 hours	No	1.2 mg. 0.4 mg.	42 minutes
10	56	M	?	None	8 hours	No	1.2 mg.	6 minutes
11	46	M	Yes	Acute alcoholism and quinidine	48 hours	No	1.6 mg. 0.4 mg.	85 minutes
12	23	F	No	Pneumonia	1 hour	No	0.8 mg.	18 minutes
13	16	F	Yes	None	11 hours	No	0.8 mg.	12 minutes
14	29	F	No	1 day post partum	8 hours	Yes	1.2 mg.	14 minutes
15	33	F	?	Rheumatic heart disease	9 hours	No	1.2 mg.	28 minutes
16	28	M	No	During abdominal exploration	10 minutes	No	1.6 mg.	6 minutes
17	39	M	Yes	None	8 hours	No	1.2 mg.	22 minutes
18	28	M	Yes	None—patient had moderate dose of quinidine	20 hours	No	1.2 mg. 0.4 mg.	34 minutes
19	32	M	Yes	Neurocirculatory asthenia	2 hours	No	1.2 mg.	8 minutes
20	27	M	Yes	None	7 hours	No	1.2 mg.	16 minutes
21	24	M	Yes	None	16 hours	No	1.2 mg.	5 minutes
22	36	M	Yes	Cirrhosis	1 hour	No	1.2 mg.	2 minutes
23	32	M	Yes	None	2 hours	No	1.2 mg.	8 minutes
24	34	M	No	2 days post operative (nephrectomy)	4 hours	No	1.2 mg.	8 minutes
25	25	M	Yes	None	5 hours	No	1.2 mg. (digitoxin)	30 minutes
26	60	F	No	Arteriosclerosis	1 week (plus)	Yes (marked)	1.6 mg.	30 minutes

patients was 35 years. There were two patients below 20, ten from 20 to 30, seven from 30 to 40, three from 40 to 50, and four from 50 to 75, these consisted of 17 males and 9 females. Nine patients had never had a previous attack, 15 had had one or more previous attacks, and in two patients we could not be sure from the history whether or not other attacks had occurred. In 13 of the cases there was no coexistent disease. Two had neurocirculatory asthenia, two had arteriosclerotic heart disease and one each had the following conditions: chronic cholecystitis, pulmonary embolism, acute alcoholism, pneumonia, rheumatic valvular disease, cirrhosis of the liver. One was one day post partum, one developed an attack during anesthesia while undergoing an abdominal exploration for a stab wound of the liver and diaphragm, and one was two days post operative following a nephrectomy.

The average duration of the attack was nine hours; however, this is omitting one extreme case from the series: that of a woman who had been in an attack for slightly over one week when seen by us.

The case of shortest duration was that of an orderly on the wards at the hospital who had had frequent previous attacks and who reported to us about 10 minutes after the onset of his attack.

Four of the patients were in clinical congestive heart failure when they were seen. All four had other disease in addition to the tachycardia. Two had arteriosclerotic heart disease, one had a pulmonary infarction, and the other who was one day post partum had evidence of preëclampsia.

The average dose of Lanatoside C was 1.2 mg. The smallest dose was 0.8 mg. and in one man as much as 2.0 mg. was necessary before the abnormal rhythm was stopped.

The average time required for conversion to normal was 19 minutes. In no case was there failure to convert to normal.

Discussion

The average age of the patients may be misleading since 11 of the cases were from the army and a Veterans Administration Hospital where the average age was somewhat less than that in a general hospital. On the other hand, since the disease does occur in infants and children and that group is not represented in our study the two factors probably cancel.

In our study there seemed to be no underlying disease which especially predisposed to paroxysmal tachycardia. Attacks which had persisted over long periods of time seemed more refractory to treatment than the average case.

Toxic symptoms after Lanatoside C were not seen in any case. Mild nausea was experienced by two patients, both of whom had received 1.6 mg. of the drug. The patient who received 2.0 mg. was nauseated and vomited, but this is hard to evaluate since he was intoxicated at the time and had vomited before receiving the drug. His case was also complicated by previous administration of very large doses of quinidine. The nausea in the

other two patients was mild and of short duration, the longest lasting about 15 minutes. For this reason we feel that this drug, in the dosage recommended, is non-toxic and relatively free from unpleasant side effects.

The signs of congestive heart failure had completely disappeared in 12 to 24 hours after the arrhythmia was controlled in all four cases in whom it was noted. No treatment other than Lanatoside C was given these patients.

Since the tachycardia was so easily and quickly controlled in these cases it is felt that this method of treatment is the one of choice in this condition. The drug is safe to administer both in the home and in the outpatient department of the hospital. It should never be given, however, without electrocardiographic control, since at times it is impossible to differentiate auricular and ventricular tachycardias clinically. The drug is of course contraindicated in any ventricular rhythm.

It might be noted that the drug is advocated only for the treatment of acute attacks. The best prophylactic drug is probably quinidine, although digitalis will control some patients.

While this study was being carried out, Weisberger and Feil [1] reported the use of Lanatoside C in paroxysmal tachycardia in 16 patients with results comparable to ours. Recent studies on the use of neosynephrine in the treatment of this disorder have been reported by Youmans et al.[2] Since reversion of the abnormal rhythm is more rapid with this latter method of treatment, further study may prove it to be the treatment of choice.

Summary

Twenty-six patients with paroxysmal supraventricular tachycardia which was refractory to vagus stimulation were treated with Lanatoside C intravenously in dosages averaging 1.2 mg. The arrhythmia was stopped in all cases within one and one half hours. Lanatoside C proved non-toxic and relatively free from unpleasant side effects.

Lanatoside C is the drug of choice for the treatment of the acute attack of paroxysmal supraventricular tachycardia at the present time.

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VISUALIZATION OF SKIN VEINS WITH THE USE OF DARK-ADAPTOR GLASSES*†

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For the past several years it has been our practice, during the course of the general physical examination of a patient, to conduct the inspection first, and then to put on dark-adaptor goggles and continue with the remainder of the examination. In this way, when, at the termination of the physical examination, we proceed to fluoroscope the chest our vision is satisfactorily dark adapted. No further time need be wasted in the darkness of the fluoroscopic room waiting for satisfactory dark adaptation, without which proper fluoroscopic examination is not feasible.

While examining patients as we wore these glasses we have frequently been impressed with our ability to see superficial venous structures of the integument which were not readily visible to the naked eye. In patients with striking integumentary venous patterns, quite prominent when the examiner wears dark-adaptor glasses, and invisible or almost invisible when the examiner inspects with the naked eye, the difference in appearance is much like that recorded in infra-red photography as against conventional photography.[1]

The inspection of relatively large, palpable, subcutaneous veins of the order of magnitude and depth of those at the bend of the elbow is not aided in any way by the device alluded to, but more superficial and smaller venous structures are strikingly delineated. The dark-adaptor glasses obviously filter out the blue rays (figure 1) reflected from the blood in the veins, and as a result, such veins appear as very dark structures. The lower the oxygen content of their contained blood, and the more distended they are, the more vivid will they appear. Veins which are deep enough to be covered by a thickness of skin and subcutaneous tissue sufficient to obscure their blue color will not show up to advantage if dark-adaptor glasses are worn.

In several patients with hepatic cirrhosis, superficial veins over the abdomen and lower part of the chest were easily visualized with the wearing of the goggles, when even careful inspection with the naked eye failed to reveal their presence. Even when collateral venous structures can be visualized by the naked eye their increased sharpness, with the use of the dark-adaptor goggles, enables more satisfactory determination of the direction of blood flow, a matter of some importance in diagnosis.

For the determination of direction of blood flow we employ the digital method in common usage.[2] A vein is selected along whose course, for a

* Received for publication May 27, 1948.
† We use Polaroid Dark-Adaptor Goggles.

short distance, there are no branches. From this segment (vividly seen as a dark structure through dark-adaptor glasses) the blood is expressed by pressing two fingers close together down on the structure, and then drawing these fingers apart, pressure being maintained by each. When several inches of vein have been emptied, one of the fingers is removed, and the refilling time is noted. The procedure is repeated, the other finger being taken off this time. It is then easy to decide whether the vein fills from below upwards or from above downwards. Normally the blood flows from above downwards in the veins of the lower two-thirds of the abdominal wall; when the blood flow is from below upwards in these veins there is almost certainly obstruction of the inferior vena cava. The blood which is unable to return by it finds a collateral circulation via the superior vena cava.

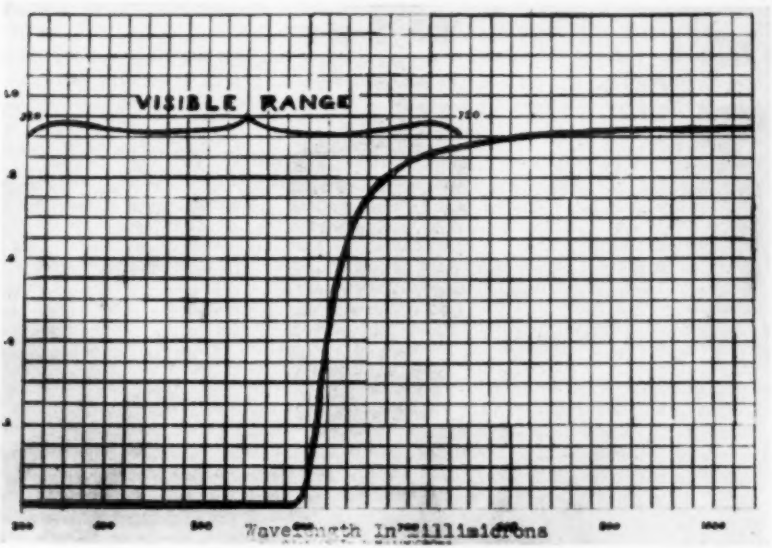

FIG. 1. Illustrating selective transmission of spectrum through dark-adaptor lenses, with exclusion of all wave lengths below 600 millimicrons.

The same hydrodynamics obviously apply in the integument following obstruction in other large veins. Thus, in obstruction of the superior vena cava, one looks for collateral veins on the chest wall. In such an instance, using dark-adaptor goggles, one can visualize small superficial venous collaterals not readily seen by the naked eye. In addition, one may more readily determine the direction of blood flow in these veins. If the current is from above downwards evidence is strong that obstruction of the superior vena cava exists. In obstruction of the innominate vein better visualization

of small venous patterns and the direction of blood flow within them may disclose unilateral venous collaterals of the integument which might otherwise be overlooked.

Of interest is the fact that abdominal striae (as seen in Cushing's syndrome and in pregnancy) are, as with the veins already referred to, much more vividly visualized than with the naked eye.

This method of visualizing veins, simple as it is, has several advantages over infra-red photography. First is the fact of simplicity and the almost negligible time involved in the procedure. Secondly, observations as to blood flow can be made. This is information which infra-red photography cannot provide.

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CASE REPORTS

THE EFFECT OF AMINOPTERIN AND PARTIAL EXSANGUINATION TRANSFUSION ON A CASE OF ACUTE STEM CELL LEUKEMIA; A CASE REPORT AND REVIEW OF THE LITERATURE ON THESE TWO PROCEDURES *

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It is the purpose of this paper to present the clinical and hematological response of a case of acute stem cell leukemia to aminopterin and to partial exsanguination transfusion.

The treatment of leukemia entered a new phase with the advent of the antifolic acid substances. These have been discussed by Farber [1] and more recently by Dameshek.[5] Also, there have been several reports of the effect of transfusions of whole blood [6, 7] and of plasma [2, 4] on the natural course of leukemia. Some of the effects of both aminopterin and partial exsanguination transfusion are exhibited in the following case.

Case Report

A 21 year old white male was admitted to hospital September 21, 1948, complaining of loss of appetite, weakness and dizziness and a non-productive dry cough for one week. Physical examination at that time revealed evidence of recent weight loss, a small, hard fixed mass of lymph nodes in the right supraclavicular fossa, the tip of the spleen just palpable, and an oral temperature of 100° F.

A roentgenogram of the chest showed some broadening of the mediastinum while a barium series suggested enlarged lymph nodes extrinsic to the upper gastrointestinal tract. Blood count showed 18,200 white blood cells of which 30 per cent were undifferentiated "blasts" and hemoglobin was 90 per cent. Sternal marrow biopsy was done three days later (September 24) and the differential count is shown in table 1. It is possible that this case resembles what Wintrobe has so aptly named a "hiatus leukemia" in that while the marrow contained 70 per cent blast cells, the remainder of the granular series precursors were not in any way increased from the normal range.

From September 24 to October 31, without any treatment, the patient's condition gradually became worse. He became much weaker, was dizzy with very little movement and had frequent episodes of vomiting. During this time his hemoglobin decreased steadily as is shown in figure 1. On October 31, he was given .5 mg. of aminopterin intramuscularly and 1.0 mg. daily thereafter for 26 days, with the exception of November 12, 13 and 14 when he developed several small circular ulcers across the soft palate and on both anterior pillars. These had cleared up by the fourteenth under local treatment and the aminopterin was re-started. Aside from these oral manifestations of toxicity the drug had no other untoward effects. The

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relationship of aminopterin to the white blood cells, number of blasts, hemoglobin, and red blood cells is shown in figure 1.

On December 2 a partial exsanguination transfusion was done, 4,520 c.c. of the patient's blood being removed with the simultaneous infusion of 5,545 c.c. of normal donor blood. The patient was bled of 950 c.c. of blood before any donor blood was started and the exsanguination was completed when only 4,300 c.c. of donor blood had been infused. The entire procedure took about two and one-half hours. No aminopterin was given from December 2 until December 21 at which time it was given as 1.0 mg. once a week. The day following the exsanguinal transfusion the patient was able to sit up in bed without dizziness for the first time since admission and the following day was able to get out of bed and sit in a chair. A bed sore, 5 cm. in

TABLE I

Sternal Marrow Biopsies

Total Nucleated Cell Count	Sep. 24 85,000 %	Oct. 31 94,000 %	Nov. 6 90,000 %	Nov. 15 20,000 %	Dec. 2 14,300 %	Dec. 11 35,000 %	Jan. 12 168,000 %
"Blasts"	70	80	79	84	46	64	97
Promyelocytes	0.3	0.5	0	0.3	0	2.3	Rare
Myelocytes	0.5	0	0	0	0	1.3	0
Metamyelocytes	0.3	0	0	0	.2	0.6	0
Polys. young neut.	6.5	1.5	4.2	1.0	11	6.0	1
Polys. mature neut.	10.0	2.0	4.2	2.5	29	6.3	1
Eosinophiles	1.0	0	0	0	0.2	0.3	0
Basophiles	0	0	0	0	0	0.3	0
Plasma cells	0	0	0	0	0	0	0
Disintegrated	7.0	15	10.6	5.0	3	8.0	20
Lymphocytes	4.0	1.0	2.0	4.5	11	3.0	1
Lymphocytes immature	0	0	0	0	0	0	0
Monocytes	1.0	0	0	0	0	1.0	0
Monocytes immature	0	0	0	0	0	0	0
Megaloblasts	0	0	0	0	0	0.3	0
Erythroblasts	0	0	0	0.3	0	1.3	0
Normoblasts	0	0	0.2	2.3	0.6	4.3	0
Megakaryocytes	0	0	0	0	0	Rare	0
Platelets	Rare	Rare	0	0	0	Rare	0

The percentages represent the differential count of 300 cells on each occasion: September 24—admission; October 31—at the start of aminopterin therapy; November 6—after a week of daily aminopterin; November 15—after two weeks aminopterin; December 2—prior to exsanguination transfusion; December 11—ten days after exsanguination transfusion; January 12—six weeks after the cessation of daily aminopterin.

diameter, that he had had for the past two weeks began to heal and his temperature returned to normal within two days. This elevated temperature had come on coincident with the breakdown of the pressure sore on his left hip. He also began to gain weight, had a marked improvement in appetite and felt very well. Chest roentgen-ray on December 20, 1948, showed that the widening of the superior mediastinum had decreased. His spleen was no longer palpable and the lymph node mass in the right supraclavicular fossa had decreased in size. He was discharged December 21.

He was re-admitted February 1, 1949, for another exsanguination transfusion. He had had a continuous epistaxis for 48 hours prior to admission and his hemoglobin was found to be 46 per cent. Blood urea nitrogen was 32 mg. per cent, albuminuria of 0.1 per cent was present and his blood pressure that had been normal on discharge was 170 mm. Hg systolic and 110 mm. diastolic. Also it was found that he had a left

pleural effusion which on aspiration turned out to be almost all blood. The following day he became very dyspneic, his pleural effusion or hemothorax was found to have recurred and it was decided that he was not able to withstand a second exsanguination transfusion.

He died on February 21. Postmortem findings were essentially as expected. Leukemic infiltrations were found in kidney, spleen, liver and lymph nodes. There

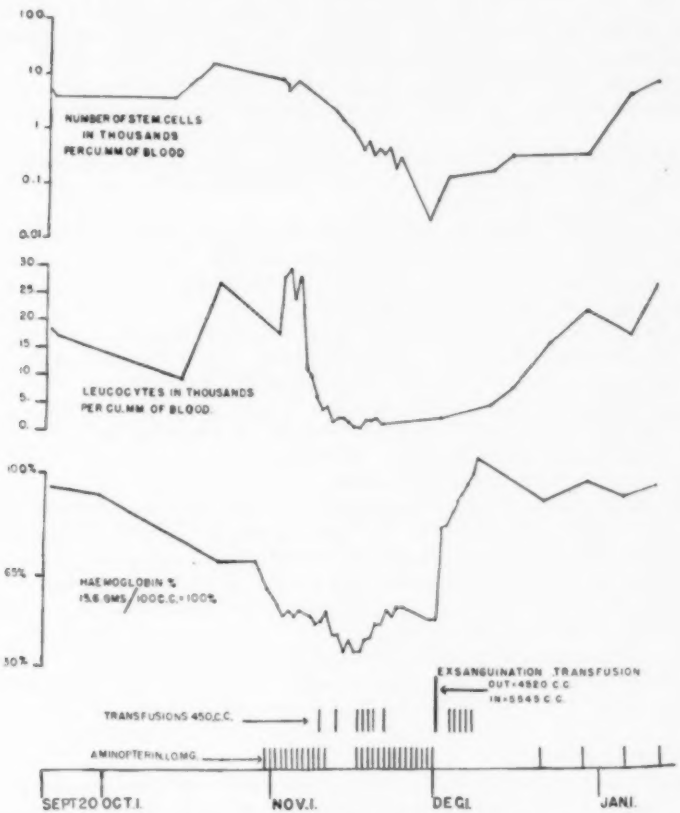

FIG. 1. The top curve represents the number of stem cells per cu. mm. of blood. As these varied from 10 to 18,000 the abscissa is plotted as the logarithm of the number. The middle curve represents the number of leukocytes per cu. mm. of blood while the lower one represents the hemoglobin.

was a mass of matted lymph nodes in the superior mediastinum as well as along the mesentery of the stomach. There were particularly extensive leukemic infiltrations in the cortex of the kidneys. It is possible that these were responsible for the clinical signs of renal failure noted on his second admission.

Discussion

Before discussing this case it is desirable to mention some of the earlier work with aminopterin and exsanguination transfusions. The original report on the effect of aminopterin was by Farber.[1] His approach to the subject was based on observations made while treating a group of acute leukemias with folic acid derivatives. These were pteryltriglutamic acid (teropterin) and pteryldiglutamic acid (diopterin). Both of these drugs were found to produce what Farber calls an acceleration process in the disease. That is, compared with a group of acute leukemias not so treated, the ones that received the folic acid derivates were found to die in a shorter time and the leukemic process on postmortem examination was found to be much more widespread in the viscera and bone marrow.

After this fact had been established and when a series of folic acid antagonists was made available by SubbaRow [1] one of them, aminopterin, was tried on five cases of acute leukemia in children.

The conclusions drawn by Farber were that aminopterin produced a temporary remission in the clinical, hematological, and histological picture of the five cases. He emphasized that the remissions are temporary and also mentioned that the drug is not without toxic side effects.

Dameshek [5] also has issued a preliminary report on the use of a number of folic acid antagonists in adults. His findings and conclusion are generally the same as those of Farber.[1] He has found that only about one-third of all types of leukemias respond, that the best results were most often found in the lymphoblastic type and least often in the monocytic type. Further, he states that despite maintenance therapy, the leukemic process finally reaches a point which prohibits further use of the drug and the patient dies.

The effect of normal blood on leukemic cells has been demonstrated both in vitro and in vivo. Timofejewsky and Benevolnskoja [2] as well as Houghton [2] have demonstrated that myeloblasts from patients with acute myeloblastic leukemia will mature as normal polymorphonuclear leukocytes in tissue culture with normal plasma as the medium. A similar result has been obtained by Israels.[3] These authors infer that the essential defect in leukemia is the absence of a maturation factor apparently present in normal blood.

Sabin et al.[4] have reported the effect of whole blood on the leukemic myeloblast in vivo. They found that following whole blood transfusions the percentage of myeloblasts in the peripheral blood diminished while the percentage of early myelocytes increased.

Bessis and Bernard [6] report striking hematological and clinical changes in a case of acute lymphoblastic leukemia following an exsanguination transfusion. One partial and two complete exsanguination transfusions were performed on a six year old child who was moribund. Following the third procedure, the pallor, fever, and purpura disappeared, and the liver, spleen, and lymph nodes diminished in size and finally became completely normal.

Piney [7] has had a similar result in a case of acute blast cell leukemia.

More recently Schwind [2] has treated two cases of acute myeloblastic leukemia in children with fresh plasma. He used the differential white cell count of the peripheral blood as his criterion for the effectiveness of treatment. In both

cases he has observed a decrease in the number of circulating myeloblasts and an increase in the number of myelocytes. The results were temporary and quantitatively related to the amount of plasma given.

In the second case, in an attempt to determine what the active principle is in normal plasma, two injections of 17 per cent gamma globulin were given. This is equivalent to the amount of gamma globulin in a 500 c.c. plasma tranfusion. These were without effect. This patient was also given a 250 c.c. infusion of commercial dried plasma. This also was without effect.

Further in support of this concept of leukemia is the work of Dreyfus [7] who after a careful and extensive study of the literature of remissions in acute leukemia has shown that there is a direct relationship between the incidence of remissions and the number and size of blood transfusions.

In our own case the effect of aminopterin on the white blood cells became manifest after nine doses had been given as is shown in figure 1. The white blood cells decreased from approximately 25,000 to a low of 800. During the period from admission to the beginning of aminopterin therapy the white blood cells varied from 18,000 to 29,500. It can be seen from figure 1 that as long as aminopterin was continued the white blood cells remained at about 2,000. However, within a week after the cessation of aminopterin the white blood cells had risen to 4,500 and continued to rise despite the weekly administration of the drug. Also the number of blast or stem cells per cubic mm. of peripheral blood varied in an approximately parallel way with the total white cell count. It can be seen from figure 1 that the number of stem cells like the total white cell count remained reduced only as long as the drug was given daily and that weekly administration really had no effect.

The hemoglobin (figure 1) which was 95 per cent on admission decreased steadily during the control period from admission, September 21 to October 31. Although the patient was not bleeding at this time, this reduction was associated with the absence of red cell precursors in the sternal marrow biopsies on either of these two occasions. Because of this profound anemia and because no megaloblast regeneration was evident after a month of daily aminopterin it was decided to do an exsanguination transfusion. This provided a means of restoring the hemoglobin to a normal level with a minimum of discomfort to the patient and in the shortest possible time. The effect of the exsanguination transfusion of course was to increase the hemoglobin markedly. The small single transfusions that were given after the exsanguination transfusion were done so as to bring the hemoglobin to 100 per cent.

Table 1 demonstrates perhaps the most significant aspects of the results of the transfusion. The admission bone marrow aspiration of September 24 shows 70 per cent blast cells with a decreased number of granular series young forms. Also there are no red cell precursors present at all (each of these marrow differential counts is the percentage of 300 cells counted). After a control period of five weeks during which time he received no treatment the change in the differential count is towards a more pathological marrow (October 31). After six days of aminopterin (November 6) there has been a slight regeneration in mature and immature polymorphonuclear leukocytes and a non-significant increase in normoblasts (.2 per cent). Further at the end of a month of daily aminopterin (December 2) it was found that the total nucleated count was reduced in the mar-

row as in the peripheral blood (figure 1) and the percentage of blasts in the former had been reduced to 46 per cent. However, there was no sustained regeneration in promyelocytes, myelocytes or metamyelocytes. The mature and immature polymorphonuclear leukocytes did reappear in significant number though. Unfortunately there was no reappearance of red cell precursors.

The marrow differential of December 11 is of special interest and is in essential agreement with the work of Sabin [4] and Schwind.[2] This biopsy was done 10 days after the partial exsanguination transfusion.

Although the total nucleated cell count at this time as well as the percentage of blasts had risen above the December 2 reading, there is a far more complete and evenly distributed reappearance of all stages of immature granular cells. Further this was the first time that red cell precursors in all three stages reappeared in the marrow. The marrow of January 12 shows the picture of complete relapse; all treatment except weekly injections of aminopterin have been discontinued since December 2.

Conclusions and Summary

1. 4-aminopteryl-glutamic acid (aminopterin) was administered to a case of acute stem cell leukemia in a young adult and was found to reduce the white blood count to normal limits and decrease the absolute number of stem cells from 18,000 per cu. mm. of blood to 16 per cu. mm. of blood.

2. Aminopterin had proportionately the same effect on the sternal marrow as on the peripheral white blood count.

3. A partial exsanguination transfusion had a far greater effect on the reappearance of normal cells in the marrow than did aminopterin, particularly red blood cell precursors.

4. Neither procedure produced a permanent remission and aminopterin was ineffective in doses administered at weekly intervals.

5. Aminopterin caused toxic side effects (oral ulceration) in this case.

Aminopterin was supplied through the courtesy of the Lederle Laboratories Division, North American Cyanamide Limited.

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SYNDROME OF NEUROMYELITIS OPTICA: A CASE REPORT WITH NECROPSY FINDINGS *

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Albutt in 1870 [1] first alluded to the syndrome of neuromyelitis optica as a separate and hitherto undescribed condition. This author stated that among five of his patients with acute myelitis, "one had eye disorders." Erb [2] in 1897, reported a case of "myelitis transverse dorsalis with neuritis descendis opticarum" in which he gave the first description and clinical analysis of the disorder. Devic [3] and his pupil, Gault, published the first complete essay on this disease, for which Devic suggested the name "neuromyelitis optique" or "neuroptica myelite." Because of Devic's important contribution this syndrome has been referred to as Devic's disease.

As the name implies, this syndrome is characterized by symptoms referable to the optic nerve and spinal cord. This combined involvement occurs not only in this disease, but also in other disorders of the nervous system as well, principally in multiple sclerosis, syphilis and encephalomyelitis. However, only in this instance is the morbid process so limited to the spinal cord and optic system that some authors have attempted to classify this combination as a complete and separate entity. In the past there has been a tendency to divide the demyelinating processes of the nervous system into four major types. According to Brain [4] and Berliner,[5] these include multiple sclerosis, Schilder's disease, acute disseminated encephalomyelitis and neuromyelitis optica. Even this division is open to criticism, because there are many neurologists who believe that these designations apply to the same disease in its different manifestations. However, there are many neuropathologists, among them Hassin,[6] who find fundamental distinctions between these various disease processes. By far the greatest number of authors including Marburg,[7] Putman [8] and Forester believe that neuromyelitis optica is related to multiple sclerosis. Fetterman and Chamberlain [9] stated in 1940 that the distinction between neuromyelitis optica and multiple sclerosis is merely the time element, rather than an actual difference in the etiologic agent or pathological process. Thus in spite of the considerable data available, there is still doubt as to whether the disease should be considered a distinct clinical entity or a specific localization.

Without attempting to resolve this dispute, it may be pointed out that the central nervous system, like certain other tissues such as collagen, can react in only a limited manner. It may degenerate, proliferate, do both, and may be complicated by hemorrhage. The lipoid material liberated from the degenerating myelin may add to the reaction. Gliosis like fibrosis usually indicates chronicity. Consequently, the pathological changes seen afford little help in deciding whether the above disease processes are separate entities or whether they are identical as to etiology, the tissue changes found and the symptoms produced being due to the location, the duration and rate of progress of the lesions and possibly modified by the age of the patient.

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Almost all authors have agreed on an infectious toxic agent as the most probable cause Milan, Lhermite, Schaffer, Horowitz [10] and others suspect a hitherto unidentified virus with neurocytotropism, or its allied toxins, as the most likely cause; however, all attempts to isolate the virus have been unsuccessful. Redlich [11] and Pette [12] include this disease in the class of disseminated encephalomyelitis and they also believe it is caused by an unrecognized virus.

The onset of the disease is usually acute or subacute and is ushered in by symptoms referable to one of the two neural structures involved. Rarely are the two structures involved simultaneously. Goulden [13] who studied many cases stated that as a rule one eye is involved by the disease process, followed by involvement of the other eye, the interval varying from a few hours to a few weeks. Beck [14] in contradiction to this statement observed that in the majority of his 70 cases, the signs of spinal cord involvement preceded the visual changes. According to Silbermann,[15] of greater importance than the chronological priority is the interval between the onset of the optic and the spinal signs. This varies from a few hours to as long as six to eight months. An interval of over one year should arouse doubt, for in all probability one is then dealing with an atypical form of multiple sclerosis, with which Devic's disease is so often confused.

Objective and subjective signs are dependent upon the structures attacked. The optic system may show all the well known pictures of primary and retrobulbar neuritis with their consequences. Various forms of hemianopsia and total amaurosis are found. The spinal cord changes are the result of either isolated appearances or various combinations of upper or lower neurone lesions. Associated with them is a great variety of sensory disturbances; frequently a sensory level is present in the upper thoracic segments, and when the myelitis occurs first, sensory symptoms may be the first to appear. Brown-Sequard's syndrome and diffuse myelitis have been described. Serious problems in nursing care arise from impairment or loss of spinal vasomotor, vesical and rectal centers. The local signs may be aggravated by general symptoms such as fever with or without increase in white cells.

The spinal fluid pressure is not increased and no block is present in the majority of cases. McIntyre [16] in 1942 reported a case associated with a spinal block from a so-called cystic arachnoiditis, and Silbermann [15] reported a similar case in 1945. The fluid may be clear, slightly cloudy or show various hues of xanthochromia. The protein content is usually increased above the normal and the colloidal gold curve reveals a non-specific pattern or a typical zone curve of discoloration. Many of the reported cases show a marked pleocytosis, usually of a lymphocytic type.

The mortality rate is high, approximately 50 per cent. Death may occur in the early stages as a result of ascending myelitis with extension of the morbid process to involve the vital centers of the medulla; or later, sometimes after an interval of months, as the result of secondary complications such as uncontrollable decubital ulcers, ascending urinary infections, or pulmonary involvement. If regression takes place, complete restoration of function is possible. Remissions seldom occur, but frequently the ailment becomes stationary with residual damage. Beck [14] reported remissions in 10 per cent of his cases and Perritt [17] reported almost 50 per cent in his cases. Relapses are rare.

Case Report

A 33 year old white male was admitted to the hospital December 20, 1946, because of blindness, pain and numbness in the lower extremities, and bladder disturbances.

Past History: The patient had been a known diabetic since the age of nine years. The diabetes had been fairly well controlled by diet and insulin; however, five years prior to this admission he had had two episodes of diabetic coma because of neglect of treatment. In 1938, on a routine physical examination, he was found to have a luetic infection. He was treated continuously with arsenic and bismuth for a period of two and one-half years. In 1943, he received further treatment for approximately nine months. In September 1946, he entered a hospital for reëvaluation of his luetic infection at which time a study of his spinal fluid was made. He was told that there was no evidence of infection; however, he stated that he was given an unknown amount of penicillin.

Present Illness: Approximately six weeks prior to admission, the patient first noticed weakness, shooting pains and a feeling of numbness in the right lower extremity. Two weeks later, on November 23, 1946, he was admitted to another hospital with a five-day history of pain in the right inguinal region associated with swelling of the right testicle. At the time of admission, he had a temperature of 102° F., and appeared acutely ill. Both testicles were enlarged, firm and extremely tender. There were enlarged, tender, inguinal lymph nodes bilaterally. The prostate gland was not enlarged but there was tenderness over the right lobe. The urine showed a specific gravity of 1.033, four plus glucose, two plus acetone, 10 to 15 red blood cells and innumerable pus cells. The patient was believed to have had a prostatic abscess which had ruptured prior to admission to the hospital. He also had an acute epididymitis and inguinal adenitis. It was felt that this infection had produced a diabetic ketosis. The infection was treated with large doses of penicillin and four grams of sulfadiazine daily. There was a satisfactory but gradual improvement and the sulfadiazine and penicillin were discontinued on the fifth hospital day. The ketosis was controlled by insulin and by the fifth hospital day the urine was sugar free. On the fifth hospital day, the patient noticed a blurring of vision of the left eye and on the sixth day of the right eye and within the next few days he lost practically all vision except for strong light.

Protamine zinc insulin was given on the ninth hospital day and by the time of discharge the patient was adequately controlled with 53 units of insulin and a diet consisting of carbohydrates 300 grams, proteins 100 grams, fats 100 grams. He was discharged on December 12, 1946, the nineteenth hospital day.

Frequency, some difficulty on urination and increasing constipation persisted. He complained of weakness, shooting pains, and numbness of both lower extremities, more marked on the right. During the three days preceding the final admission, he had several involuntary bowel movements which he attributed to a laxative. He was unable to void and had to be catheterized on several occasions.

Physical Examination: Examination showed a well-developed, well-nourished, white male who appeared acutely ill. Temperature was 102° F., pulse 78, respirations 18. Both pupils were moderately dilated, and reacted sluggishly to light. The left was slightly irregular. There was almost complete amaurosis except for the ability to distinguish strong light on the left. The fundi showed a pronounced pallor of the nerve heads and a few retinal hemorrhages and exudates in the region of both maculae. There was no evidence of involvement of any of the other cranial nerves. The heart and lungs were normal. The abdomen was distended. The bladder could be felt to extend to a point midway between the umbilicus and symphysis pubis. There was definite muscular weakness in both lower extremities, more marked in the

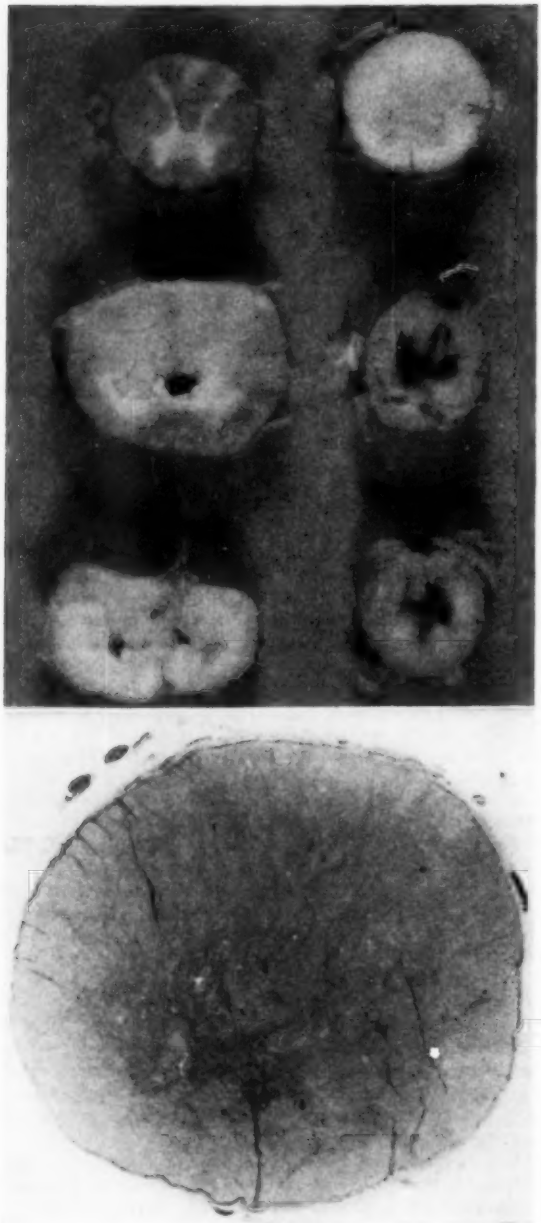

FIG. 1. *A*. Gross morbid anatomy of the spinal cord showing enlargement, softening and hemorrhage. 1. Upper cervical segment. 2. Lower cervical segment. 3. Upper dorsal segment. 4. Lower dorsal segment. 5. Lumbar segment. 6. Sacral segment.
B. Higher power view of the dorsal segment of the spinal cord.

right. There was hyperesthesia in both lower extremities below the knees. Sense of position and coördination were decreased and vibratory sense was absent below the iliac crests. Knee and ankle jerks were absent bilaterally. The plantar reflexes (Babinski, Chaddock, Oppenheim and Rossolima) were negative and the abdominal reflexes were present. Cystoscopic examination showed a congested, atonic bladder which contained 800 c.c. of residual urine.

Laboratory Findings: Urinalysis of a catheterized specimen revealed four plus sugar, two plus acetone, 15 to 20 pus cells and 8 to 10 red blood cells per high power field. The blood sugar was 310 mg. per cent. The blood Wassermann, Kline and Eagle tests were negative. Spinal puncture showed a clear fluid under normal pressure with no evidence of block. The spinal fluid showed a cell count of three lymphocytes. The spinal fluid Wassermann and Eagle tests were negative. The colloidal gold curve was 4443321000 and the spinal fluid proteins were 62 mg. per cent.

Course: The urinary infection was controlled by penicillin and sulfadiazine with continuous tidal drainage. The diabetes was managed with insulin, and on the third hospital day the urine was free of acetone and the blood sugar varied between 130 and 170 mg. per cent. He was then placed on a diet consisting of carbohydrates 250 gm., fats 100 gm., and proteins 100 gm., and given 90 units of insulin daily. During the next two weeks there was a gradual increase in the insulin requirements, and at the end of this time, he required as much as 170 units daily. Although the urinary infection and diabetes were under control, the disease process in the spinal cord progressed rather rapidly. Ten days following admission there was a complete flaccid paralysis of both lower extremities and complete loss of sensation below the fourth dorsal nerve, this nerve showing a pronounced hyperesthesia. The disease process remained stationary for approximately two weeks after which time there was a gradual spread upward involving first the left and then the right arm. The extension of the paralysis was preceded by a pronounced hyperesthesia. On January 25, 1947, the thirty-sixth hospital day, he first showed signs of bulbar paralysis, manifested by slight slurring of speech and difficulty in swallowing. Up to this time he had been mentally alert, coöperative with no evidence of mental impairment. He did develop a rather marked hyperacoustia, the slightest sound causing him considerable discomfort. During the last several days of life, he became drowsy, responded poorly to questioning and had to be aroused for nourishment. There were signs of increasing bulbar paralysis with paralysis of the deglutitory, facial and respiratory muscles and evidence of pulmonary congestion in both lung bases. On January 31, 1947, 42 days following admission, he died of respiratory paralysis.

Necropsy

The necropsy was performed one hour and 15 minutes following death. The body was that of a well-developed and well-nourished white male approximately 33 years of age. There was moderate postmortem lividity present but rigor mortis was absent.

The pleural cavities each contained a small quantity of straw-colored fluid. The right lung weighed 680 grams, the left 250 grams. The bronchi of both lungs contained a yellowish mucoid fluid. The lower lobe of the right lung showed areas of consolidation which on sectioning exuded a blood-tinged fluid. The left lung on sectioning exuded a small amount of fluid but showed no areas of consolidation. Microscopic sections through the areas of consolidation showed a variable amount of alveolar exudate consisting of polynuclear leukocytes and fluid. The pancreas was approximately one-third normal size. The parenchyma was tan in color, soft and pliable. Microscopic sections showed moderate fibrosis, associated with partial atrophy of parenchyma. The islet tissue was meager in amount, many islands ap-

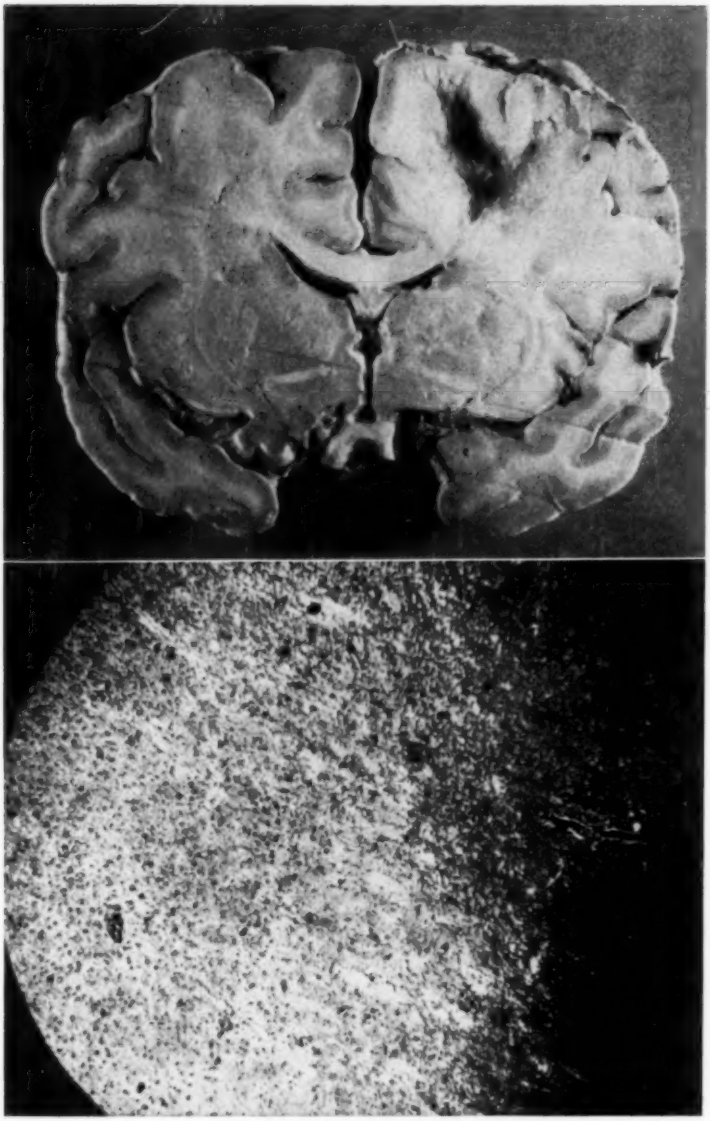

FIG. 2*A*. Coronal section of the brain showing an area of degeneration. It is confined to the white matter.

B. Higher power microphotograph of an area of cerebral degeneration. Note the relatively sharp boundary of demyelinated tissue which contains many phagocytes. Phosphotungstic acid hematoxylin stain.

pearing as only small collections of cells. The bladder was contracted, the wall measuring approximately 1.2 cm. in thickness, the mucosa being thickened and red. On microscopic section, the wall showed a rather uniform chronic inflammation. The prostate was normal in size and appearance but microscopic study showed abundant stroma and a limited number of chronic inflammatory cells.

The brain weighed 1,500 grams. The convolutions in the right parietal region were somewhat flattened. On coronal sectioning the right hemisphere contained three sharply circumscribed areas measuring 4 cm., 3 cm., and 2.5 cm., respectively, in diameter. These areas had a sharp boundary, were yellowish white in color, presented a homogeneous gelatinous appearance and were confined to the white matter. The largest area was in the parietal region and extended laterally to within 0.5 cm. of the cerebral cortex on the superior surface. The smaller areas were at the junction of the occipital and temporal lobes and were well below the surface.

The entire spinal cord was swollen. In the cervical and upper dorsal segments for a distance of 12 cm., it was enlarged to approximately twice normal size and was boggy and soft. On immediate sectioning, this part was semi-solid in consistency, but the relation of gray to white matter was unaltered. After fixation, the softened lower cervical and upper dorsal segments remained soft to a point of liquefaction and cavity formation in one area, but showed no evidence of hemorrhage. In the lower lumbar region several softened masses protruded from the surface which upon sectioning were found to be small areas of herniation. In the lower lumbar and sacral segments, several minute hemorrhagic areas were seen.

Microscopic study of the lesions in the cerebrum showed a severe demyelinizing process which was sharply limited. The border between normal and degenerated tissue was practically linear. The injured tissue formed a very loose fibrillary network which contained numerous glial phagocytes. At no point was there any damage to the blood vessels. No evidence of gliosis was detected by special stain. Aside from the lesions, the cerebral tissue revealed no changes except for a very small amount of perivascular lymphocytic infiltration in the adjacent tissue.

Myelin stains of the spinal cord showed a diffuse demyelinizing process throughout. Hematoxylin and eosin stain revealed edema and extensive exudation of phagocytic glial cells with liquefaction in the cervical and upper thoracic areas. Both the gray and the white matter were involved. The blood vessels were intact except in the lumbar and sacral segments where small areas of hemorrhage were seen. In these areas moderate perivascular infiltration of polys was observed, the only site where this type of cell participated in the reaction. There was also some infiltration of round cells. Connective tissue stain revealed no evidence of gliosis.

Microscopic sections taken from the optic nerves and the postchiasmal tracts showed no evidence of degeneration. The eyes were not examined.

Summary

This case presents the clinical syndrome which has been described as neuromyelitis optica or Devic's disease, characterized here by a rather acute onset, with initial symptoms referable to the spinal cord, followed by signs of involvement of the optic neural tract. The spinal cord involvement was initiated by sensory changes in the lower extremities, followed in approximately three weeks by signs of involvement of the neural optic tract which progressed in approximately three days to an almost complete amaurosis. The disease process in the spinal cord which first produced only sensory changes advanced rather rapidly and presented the picture of complete transection of the cord, with bilateral paralysis, total sensory loss, and absence of sphincter control. There was a rather

rapid progression upward with signs of involvement of lumbar, dorsal, and cervical segments of the cord, terminating as the result of involvement of the brain stem in bulbar paralysis.

In addition to the neural involvement, there was also present diabetes mellitus of long standing which at times had not been well controlled, as evidenced by several episodes of diabetic acidosis. There was also a history of an old luetic infection for which treatment had apparently been adequate.

The necropsy findings were those of a diffuse demyelinizing process of the spinal cord with areas of softening and cavitation accompanied by a marked phagocytic glial reaction. Some areas showed a perivascular lymphocytic infiltration but there was no evidence of glial proliferation. In addition, the right cerebral hemisphere showed three sharply circumscribed areas of demyelinization with a marked phagocytic reaction without gliosis. The pancreas exhibited marked atrophy. The prostate gland and the bladder revealed a chronic inflammatory process.

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AGRANULOCYTOSIS DUE TO PROPYLTHIOURACIL *

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THAT agranulocytosis [1, 2] and leukopenia [3] may occur during the treatment of hyperthyroidism with propylthiouracil has already been reported. We have utilized this drug in treating hyperthyroidism in a small group of patients and have encountered agranulocytosis in one instance. In order to facilitate the accumulation of statistics on the toxicity of this drug, we are reporting this latter episode. The smallness of our group renders worthless any calculation of the incidence of agranulocytosis due to propylthiouracil based on our data alone.

We have treated 27 patients with 6-*n*-propylthiouracil † for periods varying from 13 to 328 days; 26 of the group received the drug for eight weeks or more. The dosage employed was usually 100 to 200 mg. daily; five patients received a daily dose of 300 to 400 mg. during part of their course of therapy. One of this group of 27 patients developed agranulocytosis, as described below.

CASE REPORT

A white female, aged 47, complained in June, 1947 of cardiac palpitation, nervousness, and weight loss. She had undergone partial thyroidectomy for goiter 17 years previously. Physical examination in Barnes Hospital on July 3, 1947 revealed tachycardia, tremor of the fingers, ocular lid lag, and slight enlargement of the right lobe of the thyroid. The basal metabolic rate averaged plus 18 per cent.

It was decided that the symptoms could be caused by mild hyperthyroidism. Treatment with 6-*n*-propylthiouracil, 50 mg. five times daily by mouth, was initiated on July 10, 1947. Phenobarbital 30 mg. three times daily was also administered. At this time, the blood was normal; the white cell count was 7,000 per cu. mm., the differential count was 59 per cent segmented neutrophile polymorphonuclears, 39 per cent lymphocytes, and 2 per cent monocytes. The patient was told to return each week for a complete blood count and a basal metabolism test as an ambulatory patient. She failed to follow this advice, but continued to take the propylthiouracil and phenobarbital. She felt better and the throbbing sensation in her chest became less bothersome. In the middle of August she noted nasal obstruction and occipital headaches. On August 26, 1947 she reduced the dose of propylthiouracil from 250 mg. to 200 mg. daily. On September 6, 58 days after the initiation of propylthiouracil therapy, she stopped taking propylthiouracil because of a sore throat. On September 8, 1947 she was seen at home with a temperature of 39.5° C., a moderately red throat with two small patches of exudate, and cervical lymphadenopathy. She entered McMillan Hospital the next day, when the white blood count was 4,500, with a differential count of 1 per cent eosinophiles, 3 per cent myelocytes, 6 per cent juvenile polymorphonuclears, 39 per cent lymphocytes, and 51 per cent monocytes. On September 10, the white count was 4,600, with 3 per cent eosinophiles, 1 per cent myelocytes, 1 per cent metamyelocytes, 1 per cent segmented polymorphonuclear neutrophiles, 35 per cent lymphocytes, and 59 per cent monocytes. The throat culture revealed abundant beta hemolytic streptococci. On September 10, heterophile agglutinins could not be demonstrated in the blood serum in any of several dilutions, of which 1 : 20 was the lowest.

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From the Department of Internal Medicine, Washington University School of Medicine, and Barnes and McMillan Hospitals, Saint Louis, Missouri.

† The propylthiouracil was supplied by Dr. Stanton M. Hardy of Lederle Laboratories, Pearl River, N. Y.

Dr. E. H. Reinhard saw the patient, and confirmed the diagnosis of agranulocytosis; he pointed out that the monocytosis was of favorable prognostic significance in the otherwise very seriously ill patient. The patient refused bone marrow biopsy. Beginning on September 9, 100,000 units of penicillin were administered intramuscularly every three hours. Beginning on September 10, 60 mg. of folic acid were given by mouth daily. Phenobarbital and nembutal were administered by mouth throughout the hospital stay. The patient manifested fever of 39 to 40° C. for the first two days after admission, and became afebrile the fifth day. The soreness and redness of the throat persisted until September 16. The dosage of penicillin was reduced and finally discontinued after one week, as was the folic acid. The white blood cell differential count steadily approached normal; by September 15 the white count was 8,500 with a differential of 2 per cent eosinophiles, 6 per cent stabs, 56 per cent segmented neutrophile polymorphonuclears, 32 per cent lymphocytes, and 4 per cent monocytes. No abnormality of blood hemoglobin content or red cell count had been noted at any time despite repeated determinations. The patient was discharged feeling quite well on September 18. Her basal metabolic rate was minus 1 per cent of normal.

SUMMARY

A patient developed agranulocytosis and streptococcal pharyngitis 58 days after the initiation of treatment of hyperthyroidism with propylthiouracil.

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IDIOPATHIC CALCINOSIS UNIVERSALIS CUTIS WITHOUT DISABILITY *

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CALCIFICATION of the skin and subcutaneous tissues, while not common, has been reported in the literature frequently enough to offer several hundred recorded instances to medical readers. Cases of cutaneous calcification have been morphologically subdivided into two types, *calcinosis circumscripta*, in which the subcutaneous tissues in the immediate vicinity of joints, particularly of the extremities, are involved; and *calcinosis universalis*, affecting the deeper subcutaneous tissues and the dermis, usually in the proximal extremities and the pelvic girdle.[1, 7] Our case falls into the latter category, but differs from the majority

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From the Medical Service of the Presbyterian Hospital, The Department of Research Medicine of the University of Pittsburgh School of Medicine, and the Renziehausen Foundation.

of reported cases in several important respects, the most remarkable being the lack of symptomatology directly referable to the lesions. Reports in the literature are unanimous in stating that *calcinosis universalis* is a serious, and usually incapacitating disease, which frequently terminates fatally.

Case Report

A 57 year old housewife was transferred from another hospital on November 24, 1947 complaining of lumps beneath the skin of her arms and legs of five years' duration. In 1940 she noted the onset of muscle and joint pains in her extremities with associated swelling of the proximal interphalangeal joints of the fingers. The symptoms persisted with gradual regression until 1942. Following the disappearance of her muscle and joint disturbances she noted firm knobs under the skin of her arms and legs. These lumps increased in size and in hardness without any associated subjective symptoms. In 1945 the patient began to note loss of appetite and stamina. Four months prior to admission shortness of breath on exertion and swelling of the ankles appeared and persisted until she was hospitalized.

Repeated questioning failed to elicit any history of self-medication or physicians' prescriptions except for analgesics and a few small doses of oral liver powder shortly before admission. The patient and her family stated emphatically that she had not taken vitamin preparations at any time. Rapid weight loss or exposure to physical

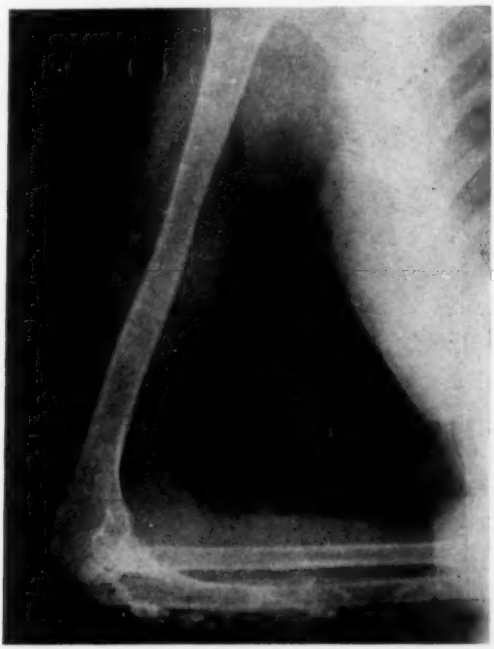

Fig. 1. Roentgen-ray of arm showing marked involvement of the forearm. The wrists and hands (not shown) were not affected. Although suggested in this print, the axillary tissues were not calcified.

trauma was denied. System review was non-contributory except for nocturia twice nightly of long standing.

The patient was born in Central Mexico, moved to Texas at the age of 29 and had lived in Pittsburgh since 1921. Two pregnancies had been uneventful. There was no known familial disease.

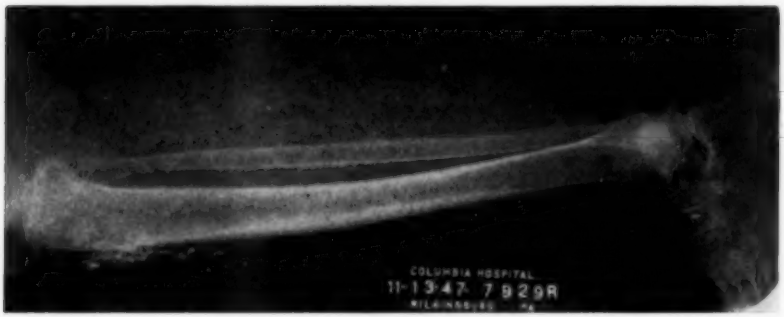

FIG. 2. Film of lower leg showing heavy calcification over the tibial tubercle and "vascular" pattern of deposits in the calf. Foot and ankle not affected.

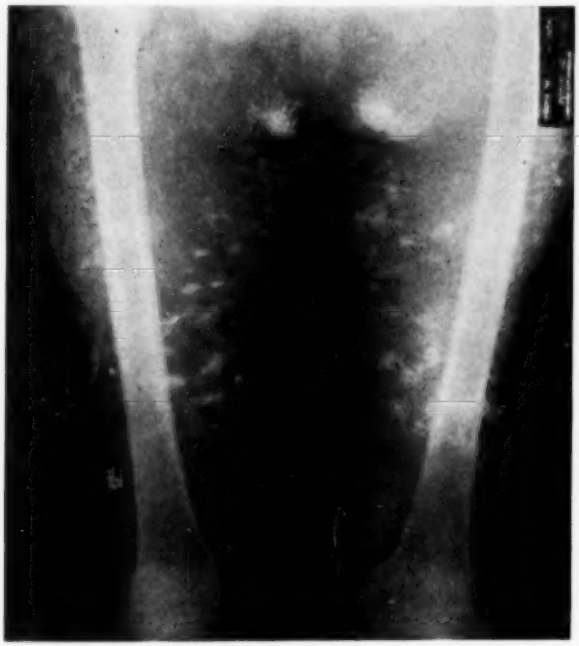

FIG. 3. Dense depositions scattered throughout upper thighs. Note sparing of periarticular tissues of knee area.

Examination revealed a swarthy elderly female with squared, Indian facies in no apparent distress but appearing to have lost considerable weight. Skin was dry and soft with underlying, freely movable, hard, non-tender, lobulated nodules in the subcutaneous tissues varying from 1 to 4 cm. in diameter. These masses seemed to lie principally in the intermuscular grooves of the arms and thighs and over the ischial tuberosities. One of them in the lateral aspect of the right antecubital space at the site of an old biopsy was fluctuant. In addition there were several softer nodules in the periumbilical area and a healing right paraumbilical scar where one of these had been removed for examination. There was a moderate, generalized lymphadenopathy.

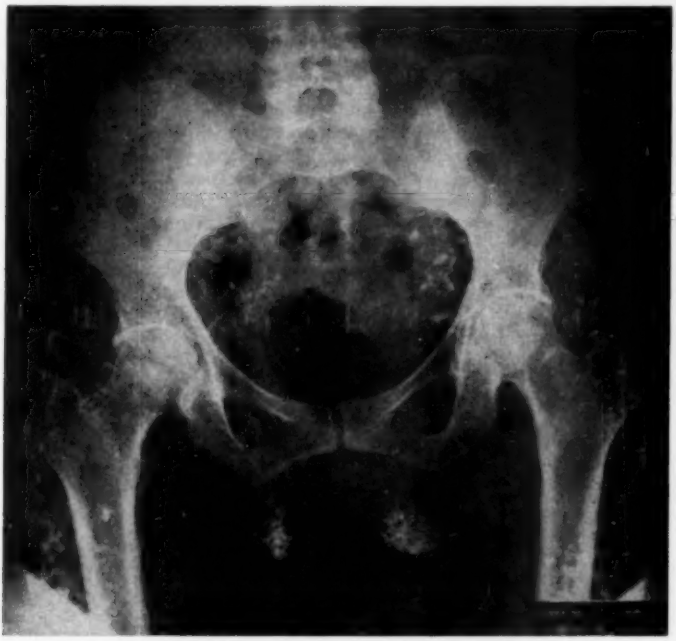

FIG. 4. Pelvic area with heavy patches over ischial tuberosities and widespread gluteal involvement.

The heart was enlarged to the left with a prolonged, loud, harsh, blowing, apical systolic murmur transmitted to the axilla with diminution of the first sound. Over the aortic area a faint, soft, blowing systolic murmur was audible. The abdomen was scaphoid and relaxed with an easily palpable, rounded, soft liver edge 3 cm. below the right costal margin, and a firm, non-tender spleen edge 3 cm. below the left costal margin. Moderate pitting edema involved the feet and lower legs.

Laboratory findings (including previous admission at another hospital): Red blood counts in October, November and December of 1947 were just over 3 million; hemoglobin rose from 6 grams at the outset to 9.5 prior to discharge. Smear revealed microcytosis and anisocytosis. White counts (three) ranged from 4,000 to 5,650 with 58 to 72 per cent polymorphonuclear cells without eosinophilia or abnormal forms.

Repeated urines showed 1 + albuminuria and occasional white blood cells with normal range of specific gravity.

Pertinent blood chemistry findings: serum total proteins 6.8 gm. per cent, albumin 2.5 gm. per cent, globulin 4.3 gm. per cent; serum calcium 11.0 and 10.7 mg. per cent, serum phosphorus 3.0 and 3.4 mg. per cent, alkaline phosphatase 4 King-Armstrong units; bromsulfalein test (5 mg. per kg. i.v.) 16 per cent retention in 30 minutes; and icterus index 12.

The following determinations were within normal limits: Blood uric acid; cephalin flocculation; blood sugar (*2*); non-protein nitrogen (*2*); Phenolsulphonephthalein; serology; blood cholesterol; intravenous galactose tolerance.

Roentgen-rays of the extremities (figures 1 and 3) revealed multiple areas of calcification in the soft tissues, some of which were clearly demarcated with lobulated contours while others showed a more diffuse and spotty pattern. These deposits were most marked in the thighs. In certain areas such as the gastrocnemius the deposits were reticulated in an almost vascular pattern (figure *2*). In addition there were deposits in the periacetabular areas and over the ischial tuberosities (figure 4). Hands and feet showed early mixed arthritic changes with little or no extra-skeletal calcification. The bones, except for the arthritic changes noted above, were everywhere normal. Films of the skull, abdomen and intestinal tract revealed no abnormalities. A chest plate showed cardiac enlargement and numerous calcified hilar glands.

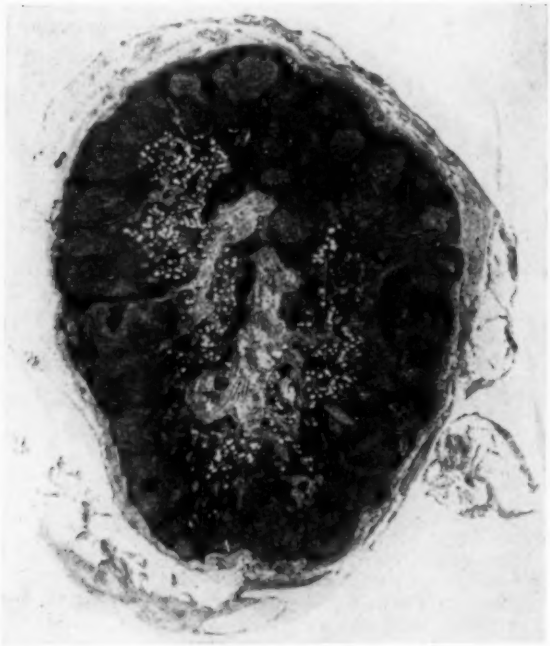

FIG. 5. Microscopic section of nodule removed from thigh. The darker area was stony hard. Tissue contained 20 per cent calcium by weight.

Biopsy of a hard lump on the right lateral thigh revealed a stony calcified nodule which on microscopic examination was typical of degenerative fatty connective tissue with large calcium deposits (figure 5). On chemical analysis it was found to contain 20.6 per cent of calcium by weight. One of the paraumbilical masses which had been removed at another hospital proved to be a lipoma.

Two studies of gastric secretions failed to reveal hydrochloric acid. Administration of large doses of parenteral liver elicited a reticulocyte response of only 3 per cent, and the total red blood count failed to rise.

The patient's course during her hospital stay was one of gradual subjective improvement. Her edema delivered spontaneously, and she was discharged after four weeks without definitive therapy.

Following discharge the patient found her activities increasingly limited by easy fatigability. Her red blood count and hemoglobin remained low and she received several blood transfusions at another hospital.

In October 1948 blood chemistries were as follows: non-protein nitrogen 30 mg. per cent, serum total protein 8.57 gm. per cent (albumin 3.05, globulin 5.52), serum calcium 9.40 mg. per cent, serum phosphorus 3.45 mg. per cent, serum ultrafiltrable calcium 5.85 mg. per cent. A Tiselius electrophoretic analysis * demonstrated 40.6 per cent γ globulin, 3.9 per cent α-1, 6.4 per cent α-2 and 7.1 per cent β with 43.8 per cent albumin. The gamma fraction pattern had a double peak.

When examined in April 1949 she seemed definitely sicker. The calcified lesions seemed more confluent, and roentgenograms showed some increase in their size. Despite this, motor function of the extremities was still adequate, and no overlying skin lesions had developed. Electrocardiographic abnormalities indicated a conduction defect suggesting left bundle branch block. Blood chemistry findings were essentially unchanged. Tiselius fractionation of proteins * showed 35.6 per cent albumin, 3.6 per cent α-1 globulin, 5.8 per cent α-2, 11.2 per cent β and 45.7 per cent γ. A double peak was again seen in the γ silhouette.

Discussion

Although the pathological calcification of mammalian tissues, particularly of connective tissue elements, is a common occurrence, little specific knowledge of the conditions which predispose a given tissue area to such changes is available.[2, 3] It is well known that arterial walls, periarticular tissues, sites of pulmonary infections, parasitic cysts and certain tumors are frequently involved by such deposits. However, abnormal calcification of virtually every body tissue has been reported.

Calcinosis universalis is most commonly seen in females,[1, 7] and unlike our case, usually affects individuals in the first two decades of life,[1, 3, 7, 11] although older victims have been reported.[7] In its typical form the overlying skin is involved in the calcific deposits and draining sinuses form when the skin breaks down.[1, 3] Disability due to pain and stiffening of the involved areas is the rule and fatal terminations are common.[1, 13] Thus our patient has, at least thus far, been fortunate in suffering an atypically benign form of the syndrome. Although forced to assume a guarded prognosis, we have no evidence that the lesions are progressing, and she herself has no complaints referable to the involved areas. In an occasional case complete resorption of the lesions has been reported in children,[1] but never in adults.

The observed calcium content of the nodule in this case is consistent with the

* The authors are indebted to Dr. Marie Fisher for performing these analyses.

findings of others.[3] The hepatosplenomegaly with laboratory evidence of hepatic dysfunction should presumably be considered to be incidental findings as others have not seen liver disorders with significant frequency in patients with this disease. This case is also unusual in that anemia is rarely seen in calcinosis.[1] However there is no reason to believe that the two findings are related in our patient.

Cases of skin calcinosis fall roughly into four etiological categories: (1) those in which lesions are the result of certain known disturbances of calcium or phosphorus metabolism such as vitamin D poisoning,[5] parathyroid disease, chronic fluorosis [12] and renal failure;[8, 9] (2) those in which calcification occurs at the site of existing infectious or traumatic insults such as parasitic cysts, old hematomas, sinuses or abscesses;[2] (3) those in which idiopathic calcification is associated with cutaneous vascular disturbances such as scleroderma or Raynaud's phenomena,[1, 4, 5] and (4) those in which no accompanying or predisposing pathology has been detected. Available data place our case in the last group.

Etiological investigations of degenerative disease of this sort are handicapped by the fact that the physician observer is obviously examining the sequelae of an initiating disturbance which was active in the remote past. Apparently the active calcification phase of the disease is an insidious one, since few if any of the reported cases have given histories of symptomatic illnesses which might have been related to the onset of calcification. Whether or not the "rheumatic" episodes reported by our patient represented the initial period of calcification cannot be determined. That illness can be explained equally well as rheumatic fever which gave rise to her cardiac lesion. The coincidence of rheumatic fever and calcinosis has not been noted. Reports of studies of calcium and phosphorus serum levels and balances have been conflicting.[1, 3, 4] Both negative and positive balances, and elevated blood calciums are reported while other workers have failed to detect any abnormalities. It is probably safe to assume that these discrepancies have arisen because some observers have studied patients during an active phase of the disturbance of calcium metabolism while the majority have been dealing with cases in whom the activating pathological process has already run its course.

The disease has been attributed to the breakdown of fat either as a result of trauma or of too rapid weight loss. Neither of these factors can be incriminated in the present instance. In general the typical distribution of the deposits (over the ischial tuberosities, tibial tubercles and dependent areas of the forearms) suggests that trauma must play some part in determining the site of these lesions, even if it is not the primary etiological factor. The frequent association of cutaneous calcification with vascular disorders of the skin suggests that the mechanism of calcification may be closely associated with circulatory integrity.[15] This has been suggested in the case of arteriosclerotic calcification following occlusion of the vasa vasorum.[16] It has also been demonstrated experimentally that damaged tissue may undergo increased calcification when serum calcium levels are artificially increased.[10] The author of a recent monograph on calcium and phosphorus in nutrition does not mention any disturbances from elevated dietary calcium.[14] In all probability some of the lesions reported are the results of previous reversible disturbances of serum calcium and phosphorus levels. Such changes may occur during transient renal insufficiency, overdosage with vitamin D, exposure to excessive concentrations of fluorides or other stimuli as yet unrevealed.

However it is not clear why the condition should progress and cause fatalities after the calcium-phosphorus balance has apparently returned to normal.

In the presence of liver disease abnormalities in serum protein fractions are to be expected. Therefore although the descending boundary electrophoretic patterns in this case are distorted, they are merely reported at this time with no attempt at interpretation.

The absence of symptoms in the case reported here seemed to render any attempts of therapy unnecessary. As in most idiopathic "degenerative" disease, countless medications have been utilized in attempts to arrest or reverse the progression of this condition. Reported results are conflicting, but in the main are unfavorable.

Summary

An unusually benign case of calcinosis universalis is reported, and the implications of this type of pathological calcification are briefly discussed.

The authors wish to acknowledge their indebtedness to Dr. W. A. Bradshaw for data pertaining to the earlier admission of this patient and to Dr. T. S. Danowski for advice and assistance.

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TOXICITY OF DICUMAROL: REVIEW OF THE LITERATURE AND REPORT OF TWO CASES *

By JOHN S. POWERS, JR., *Kingsport, Tennessee*

INTRODUCTION

SINCE the introduction of Dicumarol in 1941 its usefulness as an anticoagulant has been critically studied by many clinicians and investigators.[1-15] Initially its use was restricted to the treatment of peripheral thromboembolic disease. However, the American Heart Association has carried out an extensive investigation of its efficacy in the prevention of complications of myocardial infarction.

Wright and Foley [1] reviewed the use of anticoagulants in heart disease and gave preliminary observations concerning the large study now in progress. They stated, "Results appear to demonstrate conclusively that this form of therapy is the most satisfactory used to date." Parker and Barker [2] reported on the first 50 cases of myocardial infarction treated with Dicumarol at the Mayo Clinic. In comparison with a control group of 100 cases studied by Nay and Barnes, they found a striking reduction in all complications. The fatality rate when anticoagulants were used was 10 per cent. Falk [3] states, "Dicumarol therapy represents the first step in the formation of a positive therapeutic approach to the problem of coronary thrombosis, except for oxygen."

Anticoagulants have been extensively used postoperatively at the Mayo Clinic. A later report by Allen, Hines, Kvale and Barker [4] covers 2,307 cases. The results are quite impressive. Most striking are the figures dealing with 329 cases of pulmonary embolism. According to previous statistics the expected number of subsequent fatal emboli should have been 60. None occurred.

Evans and Dee [5] summarized 184 cases given anticoagulants at the Lahey Clinic. All had postoperative venous thrombosis with or without pulmonary embolism. They report diminution of mortality due to postoperative pulmonary embolism to one-half of previous statistics. Venous ligation has been used much less frequently—in only 10 of the above cases.

In the presence of these favorable reports, the use of anticoagulants has become progressively more widespread. Heparin seems so far to be quite innocuous. However, its expense and inconvenience continue to be such that Dicumarol, which is inexpensive and orally administered, will probably be used extensively for some time.

That Dicumarol is relatively safe when dosage is regulated by expert prothrombin determinations is attested by the fact that to date of writing only five deaths have been reported during its administration. Barker et al.[6] report three. One occurred during severe prothrombin deficiency, one before prothrombin deficiency had developed and the third after the prothrombin time had returned to normal. Wright and Foley [1] report a single death: a 47 year old white woman in chronic congestive failure who developed severe pulmonary hemorrhages during treatment with Dicumarol and in whom, at autopsy, a cast of clotted blood was found to be occluding the left main bronchus and its major branches. Shlevin [7] reports a 79 year old woman who developed hemorrhagic phenomena which led

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to her death. Autopsy revealed extravasations of blood into the brain, kidneys, meninges, and urinary bladder.

Bauerlin,[8] Thorsen,[9] Cahen,[10] Nelson,[11] Zucker,[12] Draper,[14] and Gefter et al.[15] report instances of less serious bleeding.

The anticoagulants heparin and Dicumarol have been used in the treatment of thromboembolic complications of severe medical diseases at the New Orleans Veterans Administration Hospital. Dosage has been regulated on a basis of the prothrombin concentration as determined by the method of Quick on undiluted plasma. The plan of Allen et al.,[4] attempting to keep prothrombin concentration between 10 and 20 per cent of normal, has been followed. To date there have been two hemorrhagic episodes of major severity. One patient died. It is thought that the presentation of these cases in detail might be of interest.

Case Reports

Case 1. A 55 year old white man was admitted to the New Orleans Veterans Administration Hospital on December 3, 1947. At first the patient and his relatives were unable to give a satisfactory history, stating that the patient's feet had rather sud-

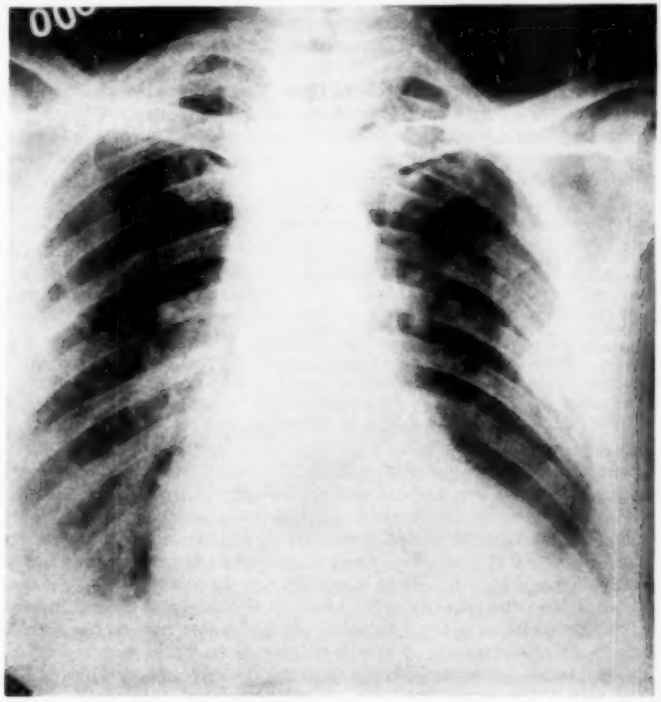

Fig. 1. A roentgen-ray of the patient's chest taken shortly before institution of anticoagulant therapy. Opacities in right lower lobe and in left lung were thought to be consistent with the clinical picture of pulmonary infarction.

denly become swollen and discolored about a week prior to admission. There was a past history of spastic paraplegia, thought to be due to disseminated sclerosis; and arterial hypertension, with blood pressures ranging about 200 mm. of mercury systolic and 120 mm. diastolic.

The patient was confused and dyspneic. His feet and ankles were markedly edematous and there was gangrene of the distal half of the dorsum of both feet and of the third, fourth and fifth toes of both feet. Heart sounds were distant. Moist râles were present in the right lung base. The liver could not be palpated. Blood pressure was 150 mm. Hg systolic and 98 mm. diastolic. Venous pressure was 140 mm. citrate. The skin and sclerae were slightly icteric. He was obviously gravely ill.

Red blood cells 4,330,000; white blood cells 17,050 (91 per cent neutrophiles, 9 per cent lymphocytes). Blood sugar, fasting, 117 mg. per cent; non-protein nitrogen 35 mg. per cent; total serum protein 6.5 gm. per cent, CO_2 combining power 52 volumes per cent; serum bilirubin 2.7 mg. per cent, prothrombin time, 12 seconds (100 per cent of normal). The urine showed a trace of albumin and 4 to 5 red blood cells per high power field. An electrocardiogram revealed a posterior infarct of undeterminable duration.

The initial working diagnosis was myocardial infarction with congestive failure and thromboembolic phenomena. The patient was given digitalis and mercuhydrin and placed in an oxygen tent. Anticoagulants were started as the measure of choice to prevent extension of the suspected thromboembolic process or processes. A left sympathetic block was performed.

Two hundred mg. of Dicumarol were given as the initial dose. Three 50 mg. doses of heparin were given at four hour intervals on the first day. Dicumarol dosage and prothrombin levels are shown below:

Date	Prothrombin Level	Dicumarol Dosage
December 3, 1947	100% of normal	200 mg.
December 4, 1947	21% of normal	100 mg.
December 5, 1947	40% of normal	100 mg.
December 6, 1947	19% of normal	Discontinued because of rectal hemorrhage
December 7, 1947	12% of normal	
December 10, 1947	50% of normal	
December 11, 1947	45% of normal	
December 18, 1947	50% of normal	
December 19, 1947	50% of normal	
December 24, 1947	55% of normal	
January 5, 1948	80% of normal	

At about 9:30 p.m. on December 6, 1947, the patient had a rectal hemorrhage of about 300 c.c. He was given a transfusion of 500 c.c. of citrated blood and started on menadione sodium bisulfite in doses of 4.6 mg. intramuscularly every four hours. On the following morning he passed about 200 additional cubic centimeters of blood per rectum. Fifty mg. of menadione sodium bisulfite were given intramuscularly and intravenously during that day. There was no further bleeding.

A few days later the patient's sister came to visit him and gave a history which elucidated the pathogenesis of the gangrene. He had rather suddenly become dyspneic seven weeks prior to admission. A few days later edema of the feet and ankles began to develop and became progressively more extensive. Home remedies had included soaking the feet in hot water and later application of hot water bottles to the sites which were gangrenous on admission. The case was reëvaluated and thromboembolic disease was excluded from the diagnosis.

After a very stormy course, thought to be due chiefly to toxic absorption from the gangrenous tissue, the patient was brought out of failure. A partial amputation of the distal portion of both feet was done with uncomplicated convalescence.

There was never any further evidence of hepatic disease and it is now thought that the slight initial icterus was due to chronic passive congestion of the liver secondary to heart failure of seven weeks' duration.

Case 2. The patient was first hospitalized on June 13, 1947, with a past history of several attacks of acute rheumatic fever in childhood and knowledge of a heart murmur for several years. He had been having an intermittent fever for about four months. A private physician had made the diagnosis of subacute bacterial endocarditis by means of blood cultures and had given the patient an undetermined quantity of penicillin without evidence of improvement.

On physical examination there was slight cardiac enlargement and grade four systolic and diastolic murmurs over the entire precordium, loudest over the aortic area. Petechiae of the palms, soles and soft palate were present and Osler nodes were observed on several fingertips. Temperature was 99°. Blood pressure 110 mm. Hg systolic and 70 mm. diastolic. Blood cultures taken on June 13 and 14 were positive for alpha hemolytic streptococcus. The patient was treated with 40,000 to 60,000 units of penicillin intramuscularly every two hours for six weeks. There was no further evidence of activity of the endocarditis, and he was discharged on September 8, 1947, after having been digitalized because of mild cardiac failure which had come on during the preceding three weeks.

He was readmitted on October 30 with the history of having developed mild dyspnea and orthopnea during the previous two weeks. The heart was somewhat larger. The systolic and diastolic murmurs were unchanged. Blood pressure 170 mm. Hg systolic and 56 mm. diastolic. Venous pressure 142 mm. of citrate. Circulation time with decholin was 40 seconds. There were a few crepitant râles in both lung bases and the liver was palpable two fingers below the right costal margin. There was no evidence of infection. Numerous blood cultures were negative.

The patient had a slowly progressive downward course with brief attacks of what was thought to be thrombophlebitis in the veins of the legs five days after admission and again four weeks later. These were treated with heparin and Dicumarol in small doses which were discontinued rather quickly because of the equivocal nature of the physical findings. During the second hospital month severe bronchopneumonia was successfully treated with penicillin and oxygen.

On January 27, 1948, approximately two months after admission, the patient suddenly developed pain in the left chest. It was pleuritic in nature and a friction rub was heard over the left chest. On the following day the friction rub over the left chest had disappeared and a loud rasping friction rub was heard over the right lower lung field anteriorly and laterally. A roentgen-ray of the chest was interpreted as being compatible with an infarct in the right lower lobe, and it was decided to give the patient anticoagulant therapy. Dicumarol was given according to the plan outlined by Allen, Barker and Hines.[1] Dosage and prothrombin levels are shown in chart 1. The patient never had definite evidence of femoral thrombophlebitis. His condition was considered too critical for femoral ligation.

On the twenty-fourth day of therapy slight epistaxis was noted and Dicumarol was discontinued. On the following day, the patient was slightly icteric and epistaxis continued. At this time the prothrombin concentration was 30 per cent of normal. The next day the prothrombin concentration fell to 7 per cent of normal and 60 mg. of Hykinone (menadione sodium bisulfite) was given intravenously. Epistaxis continued. On the following day, prothrombin concentration was 8 per cent of normal. Epistaxis was more severe and nasal packs were inserted. He was given 115 mg. of Hykinone intravenously. On the fourth day after discontinuation of Dicumarol, the

patient continued to ooze blood from the nose and was again given 115 mg. of Hykinone intravenously. About two hours later he suddenly developed severe anxiety, went into circulatory collapse and died.

Autopsy Findings: There was moderate icterus of the skin and sclerae. No petechiae were present. There was two plus pitting edema of the ankles.

Large ecchymoses were found in the pelvis along both paracolic gutters, in the region of Treitz and in the visceral peritoneum of the splenic flexure, duodenum, jejunum and sigmoid. There were large ecchymotic areas studding the parietal pericardium posteriorly and superiorly.

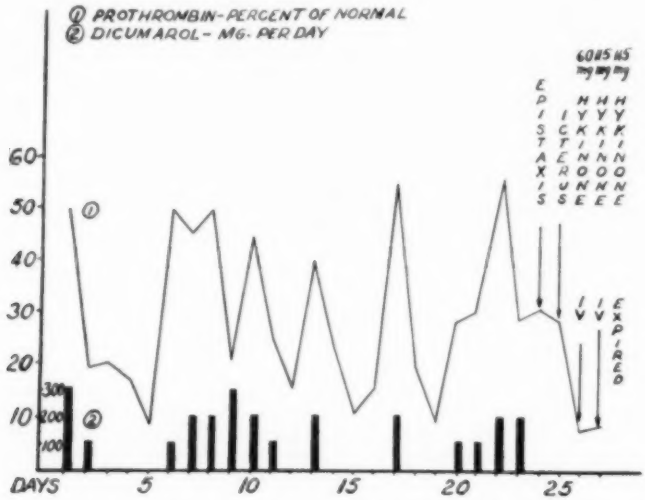

CHART 1. Depicting relationship of Dicumarol dosage to prothrombin content of plasma as determined by the Quick prothrombin time technic on undiluted plasma.

The patient developed epistaxis on the twenty-fourth day of therapy and icterus on the twenty-fifth day. He was given a total of 290 mg. of Hykinone intravenously, but died of massive hemorrhage.

The trachea and bronchi were filled with muco-sanguineous, slightly frothy liquid, predominantly blood, which completely filled the bronchial tree in all lobes, even into the terminal bronchi. There was no evidence of thrombosis or embolism. All lobes were diffusely consolidated and section revealed a diffusely hemorrhagic and firm cut surface. The liver weighed 1300 grams. The parenchyma was firm and grayish yellow with accentuation of the hepatic markings. Much blood oozed from the cut surface.

The mucosa of the renal pelves and ureters was ecchymotic. There was no bleeding into the gastrointestinal tract. No thrombi were found in the vena cava or its inferior tributaries. No postmortem clotting had occurred. A subepicardial hemorrhage was found beneath the lateral and posterior surfaces of the left ventricle. The major cardiac abnormality was found at the aortic valve. The cusps were identified with difficulty, but with certainty, and were found to be tremendously thickened and calcified, with marked stenosis. Large plaques of calcium extended into the sinuses of Valsalva and down on to the ventricular surface of the anterior mitral

cusps. These calcific plaques were warty and yellow. The left coronary orifice was surrounded by atheromatous plaques but was widely patent. There were two right coronary orifices, each measuring less than .1 cm. in diameter.

Microscopic examination of the lungs revealed diffuse alveolar filling with red cells with occasional aerated alveoli. In one area there was scarring suggesting an old healed infarct. The normal lobular structure of the liver was somewhat disorganized due to the marked congestion present. This congestion was most marked about the central veins. In these areas because of the marked congestion, atrophy of the liver cords was present. The portal spaces were essentially normal. The kidneys showed benign nephrosclerosis.

Discussion

To date only hemorrhagic complications of Dicumarol therapy have been reported. Although the gross autopsy findings indicated that case 2 had anatomical cardiac changes probably incompatible with recovery from congestive failure the immediate cause of death was hemorrhage into the lungs and retroperitoneally due to incoagulability of the blood, brought about by Dicumarol.

These two cases had in common congestive heart failure of seven weeks or longer. Both were slightly icteric, although the icterus was noted in case 2 after epistaxis had already begun. Clinical studies in the patient who survived and autopsy findings in the patient who died revealed no cause for the icterus other than chronic passive congestion of the liver secondary to heart failure. This suggests the consideration of two possible mechanisms to explain the presumed excessive Dicumarol activity leading to the hemorrhagic phenomena.

1. Chronic passive congestion of the liver interfered with the function of prothrombin formation to such an extent that administration of what had previously been safe doses of Dicumarol so severely disrupted the clotting mechanism as to cause hemorrhage.

2. Diminished renal filtration due to congestive failure [10] caused retention of Dicumarol to such an extent that toxic levels were reached.

A combination of these two mechanisms also seems entirely possible.

No definite conclusion can be drawn from these two cases. However, it seems justifiable to use extreme caution in the future when administering or planning to administer Dicumarol to patients in chronic congestive heart failure.

Summary

1. Anticoagulants are rapidly gaining a favorable reputation in the treatment of thromboembolic disease. Because of its cheapness and ease of administration Dicumarol is frequently the drug of choice.

2. Two cases are presented in which Dicumarol resulted in severe hemorrhage. One patient died. These cases had in common chronic congestive failure. Slight icterus was present prior to hemorrhage in one and after hemorrhage had begun in the other.

3. It is suggested that the toxic reactions may have been due to impaired liver function, diminished renal filtration of Dicumarol or a combination of the two.

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THE PULMONARY MANIFESTATIONS OF SCLERODERMA: AN ANATOMIC–PHYSIOLOGICAL CORRELATION *

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DIFFUSE visceral changes occurring in scleroderma have been described by Lewin and Heller,[1] Notthafft,[2] Kraus,[3] Klemperer, et al.,[4] Bevans,[5] and Weiss et al.[6] In some of these cases changes have been noted in the lungs. In most of them, however, the pulmonary findings were not a prominent clinical feature. Among the more detailed reports of lung changes in scleroderma, the review by Matsui [7] is noteworthy. Murphy, Krainin and Gerson [8] reported the first case in which pulmonary changes of scleroderma were diagnosed roentgenographically during life. This was done on the basis of diffuse reticular infiltrations in the lung associated with the more characteristic peripheral manifestations of scleroderma. More recently, Getzowa [9] reported in great detail, anatomic changes occurring in the lungs in scleroderma. This report was based upon two necropsied

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cases. However, in these cases the diagnosis during life was tuberculosis. We have recently had the opportunity at Bellevue Hospital of observing a case of scleroderma in which the clinical features were almost entirely related to the pulmonary changes. This was diagnosed correctly during life and extensive cardiopulmonary physiologic studies were performed. Fortunately, a necropsy was obtained permitting the correlation of anatomic and functional findings.

Case Report

A 65 year old white man, formerly an engineer, entered the hospital on February 6, 1946 complaining of weakness of several months' duration.

Present Illness: Patient had been in good health until about 10 years ago when he noticed shortness of breath. He gradually reduced his activities. His condition became progressively worse and was accompanied by ankle edema. About four years prior to admission he had consulted numerous physicians who had told him that he suffered from heart disease and treated him unsuccessfully with large doses of digitalis. At that time he also began to have a cough productive of a variable amount of mucoid sputum.

Two years prior to admission these symptoms led to his entering two different hospitals in New York City, the first in April and the second in June 1944. The findings in both instances were similar. The patient raised from 60 to 100 c.c. of mucopurulent sputum daily. Physical examination revealed muffled but regular heart sounds and numerous râles at the bases of both lungs. Repeated roentgenograms showed a somewhat tortuous aorta, increase of bronchovascular markings and marked congestion of the lower half of both lung fields. The electrocardiogram indicated a left axis deviation with a PR interval of 0.20, the latter being ascribed to the administration of digitalis. A normal venous pressure and circulation time and the absence of definite enlargement of the heart did not support a diagnosis of congestive heart failure. Bed rest, salt free diet and diuretics failed to produce any clearing of the lungs. There was very little improvement in the patient's general condition. He was discharged from one with the diagnosis of pulmonary fibrosis and emphysema, and from the other with undiagnosed heart disease and pulmonary emphysema, cause unknown.

During the following two years dyspnea and cough increased and were associated with progressive weakness. One and one-half months prior to admission (December 1945), he developed pneumonia. He was treated at home with penicillin. He recovered rapidly. However, his weakness increased to the extent that he collapsed one day and was brought to the hospital.

Further questioning revealed that the patient had noticed changes in the skin and joints during the past four years. At first he had experienced difficulty in writing due to inability to bend his fingers completely. Shortly afterward he found that his hands and feet frequently became cold, blue and numb. The skin over the anterior part of the chest became tight, white and itchy. These manifestations were subject to exacerbations and temporary improvement. Eventually a pigmentation appeared on his hands and forearms. The skin of the face became scaly and dry. During the past year the patient complained of pain and swelling of his wrists and elbows. He did not have any dysphagia and there was no diarrhea or constipation. His appetite, however, was poor and his weight over a two year period had decreased from 187 lbs. to 139 lbs.

Past History and Family History: The patient was born in the State of Washington, of German parents. His father died of "Bright's disease" at the age of 56, and his mother died of pulmonary tuberculosis at an early age. The patient worked first in clerical occupations, then entered the export business, and eventually, at the age

of 50, became a steam engineer. He had been a heavy drinker all his life. Otherwise the history was non-contributory.

Physical Examination: The patient was a well developed, rather thin, white man who appeared chronically ill. He was somewhat cyanotic and dyspneic at rest and became markedly distressed at the slightest effort, such as walking a few steps. He coughed frequently and produced a thin white mucoid sputum, the amount of which varied from 100 to 200 c.c. in 24 hours, depending on the moisture in the atmosphere.

On admission his temperature was 99.8°, the pulse 84, and the blood pressure 110 mm. of mercury systolic and 70 mm. diastolic. The face was dry and presented a fine desquamation. The nose and lips were thin and small. Over the anterior aspect of the thorax the skin was tight and shiny and gave a waxy feeling to touch. The skin over the extremities was also cold and tight, and could not be folded. A discrete pigmentation was present over the hands and forearms. Movements of the small joints of the hands were limited and painful. There was slight edema of the ankles. The heart sounds were clear and regular. The breath sounds were normal but numerous coarse râles were heard over the lower half of both lungs. The remainder of the physical examination was negative.

Laboratory Findings: Blood count: red blood cells 4,440,000; hemoglobin 12 gm.; white blood cells 13,000; polymorphonuclears 82 per cent; lymphocytes 9 per cent; monocytes 5 per cent; eosinophiles 4 per cent. Wassermann test negative. Sputum: *Staphylococcus aureus, Streptococcus viridans,* and a pneumococcus which did not type. Smears and cultures for acid-fast bacilli were negative. Urine: specific gravity 1.026; few white blood cells per high power field but no other abnormal findings. Stools negative for blood. Basal metabolic rate minus three.

Blood chemistry: Blood urea nitrogen 16.5 mg. per cent. Blood sugar 143 mg. per cent. Total protein 6.5 gm. A/G ratio 4.1/2.4. Cholesterol 222 mg. per cent. Esters 123 mg. per cent. Calcium 9.6 mg. per cent. Phosphorus 2.7 mg. per cent. Alkaline phosphatase 8.4 mg. per cent. Cephalin flocculation 1 plus.

EKG: There was a tendency toward right axis deviation and a PR interval of .21 with a QRS of .08. The chest roentgenogram showed a widened and tortuous aorta. The heart was slightly enlarged. In the lower two-thirds of both lung fields, there was a diffuse reticular shadow. This shadow was dense at the bases and thinned out in the middle third of both lungs (figure 1). The esophagram was normal. Roentgenograms of the hands and feet did not indicate any trophic changes.

Skin biopsy: a piece of skin was removed from the anterior chest wall on March 14, 1946 and the findings were reported as "scleroderma."

Functional Studies * March 22, 1946:

Pulmonary Function:

	Observed	Normal
Vital capacity	1,750 c.c.	4,140 c.c.
Residual air	921 c.c	1,335 c.c.
Alveolar nitrogen after 7 minutes O_2 breathing—1.4 vol. per cent		

Residual Air:

Total capacity × 100	33.4 per cent	24.4 per cent
Maximum breathing capacity 81 lit/min. (93.5 per cent of normal)		
O_2 saturation	91.1 per cent	at rest
	81 per cent	after exercise

Circulatory Function:

	Observed	Normal
Cardiac output lit/m^2 body surface/min.	5.5	3.2
Right ventricular B.P. mm./Hg.	71/3	28/0-4
Arterial B.P. mm./Hg.	118/67	–
Plasma volume c.c./m^2 body surface	1,755	1,600

* Courtesy of Dr. A. Cournand.

Course in the Hospital: During his stay in the hospital the patient's condition became progressively worse. The weakness increased and the dyspnea eventually became such that almost continuous administration of oxygen was required. The sputum remained white and mucoid but varied between 60 and 240 c.c. in 24 hours. The findings on physical examination did not change greatly, except for the appearance of persistent edema of the ankles. Repeated blood and urine examinations and roentgen-ray films failed to show any significant variation from the findings on admission. The electrocardiogram, however, underwent a definite and marked change. The electrical axis underwent a marked shift to the right. The PR interval increased from .21 to .28 and the QRS from .08 to .11. At one time digitalis and mercurial diuretics were tried without success. The course continued rapidly downward and the patient died on July 27, 1946 (the one hundred eighth hospital day).

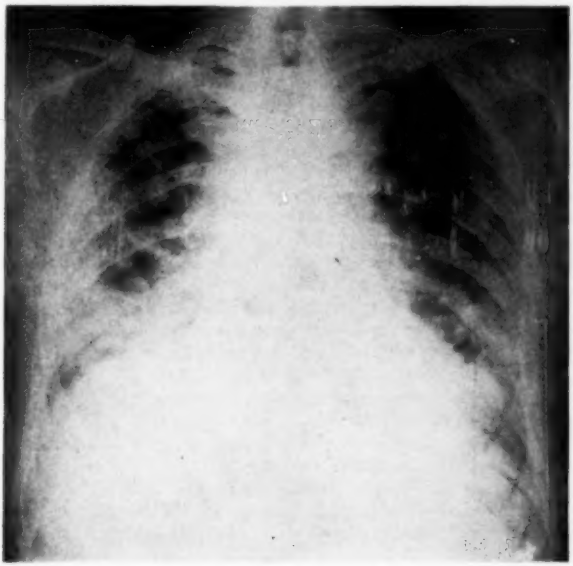

FIG. 1. Roentgenograph of lungs showing diffuse reticular changes.

Post-Mortem Findings: (The findings will be limited to those pertinent to this case.) The skin was shiny, smooth and taut, particularly over the bony surfaces of the fingers and toes, over the nose, ears and forehead. There was a fine scaly desquamation present. Over the olecranon process of the left elbow, there was a small ulceration of the skin. The hair was scant and had a female distribution on the trunk. There was a marked bluish discoloration of the distal portions of the fingers and toes. A slight brawny, non-pitting ankle edema was present. Both lungs were bound down with easily divided fibrous adhesions. There were 75 c.c. of serosanguineous fluid present in the right pleural cavity. The parietal pericardium was rather intimately attached to the visceral pericardium and the pericardial cavity was almost completely obliterated. The mediastinum appeared in the midline and no abnormal masses were found.

The heart and attached pericardium weighed 700 gm. There was a diffuse subendocardial fibrosis present in all chambers. All the valve leaflets were delicate and competent. All the chambers were dilated but the dilatation was most marked in the right ventricle. The right ventricular myocardium measured 7 mm. in thickness, while the left ventricular myocardium measured 1.5 cm. On section of the myocardium a few scattered areas of fibrosis were seen, especially in the apical portion of the interventricular septum. The coronary arteries were patent and their lumina nowhere constricted. The wall of the aorta was elastic and did not appear dilated. There were a few scattered irregular plaques in the intima of the thoracic and abdominal aorta.

The right lung weighed 900 gm., the left lung 770 gm. Both lungs were essentially similar in appearance. The pleura was everywhere diffusely granular, thickened and opaque. Some fine deposits of fibrin were present. The bronchi contained a moderate amount of thin mucopurulent exudate. The walls were intact and there was a dilatation of the smaller bronchi and bronchioles in both lower lobes. The upper lobes of both the right and left lung and the middle lobe of the right lung were almost completely consolidated and airless. The lower lobes were subcrepitant and moderately firm. On section of the lung the surface was rather dry, glistening and granular. It was irregularly deep red with a few denser areas of gray scattered throughout. Many thin-walled, cyst-like spaces were present. The size of these cyst-like areas ranged from 2 mm. to 1 cm. These were surrounded by dense zones of fibrous tissue. These cysts were most prominent towards the base and peripheral regions of the lung. The pulmonary arteries showed a moderate degree of sclerosis. The hilar tracheobronchial lymph nodes were enlarged, succulent and black.

The liver presented typical appearance of chronic passive congestion.

The gall-bladder, spleen, pancreas, adrenals and kidneys presented no gross abnormalities. The gastrointestinal tract as well showed no gross abnormalities. There were no other gross findings of any significance.

Histologic Findings: The significant sections were from the skin, lungs, heart and alimentary tract. These were stained with hematoxylin and eosin, trichrome, Weigert and van Gieson preparations.

Sections through the skin revealed a thin epidermis that was atrophic and contained a few pigmented cells in the basilar layer. Some keratin was present on the surface. The rete pegs were short, blunted and reduced in number. The dermis was made up of interlacing bands of collagenous connective tissue. Relatively few skin changes were seen. The sweat glands and hair follicles were surrounded by areas of fibrous tissue. The arteries had no significant changes.

Sections of striated muscle showed no remarkable changes.

Sections of the wall of the esophagus showed slight congestion of mucosal vessels and fibrous replacement of the muscularis propria. Other areas revealed collections of lymphoid tissue in the lamina propria. There was also slight to moderate thickening of this layer by fibrous tissue. In many areas the muscularis was replaced by fibrous tissue. In some muscle persisted as separate correlating atrophic fibers. The changes in the small arteries and arterioles were similar to those seen elsewhere.

Sections taken through portions of stomach, small intestine and large intestine revealed slight increase in fibrous tissue and replacement of muscle by fibrous tissue.

Section of heart revealed marked subendocardial fibrosis and replacement of subendocardial myocardium with fibrous tissue. There were focal areas of fibrosis scattered throughout the myocardium. In and near these areas the arterioles were thick-walled and often had rather narrow lumens. There was intimal and subintimal fibrosis with thinning of the media in some areas. In some vessels there was a pink-staining hyaline material deposited subintimally. The parietal pericardium was adherent by loose fibro-adipose tissue to the visceral pericardium and contained a

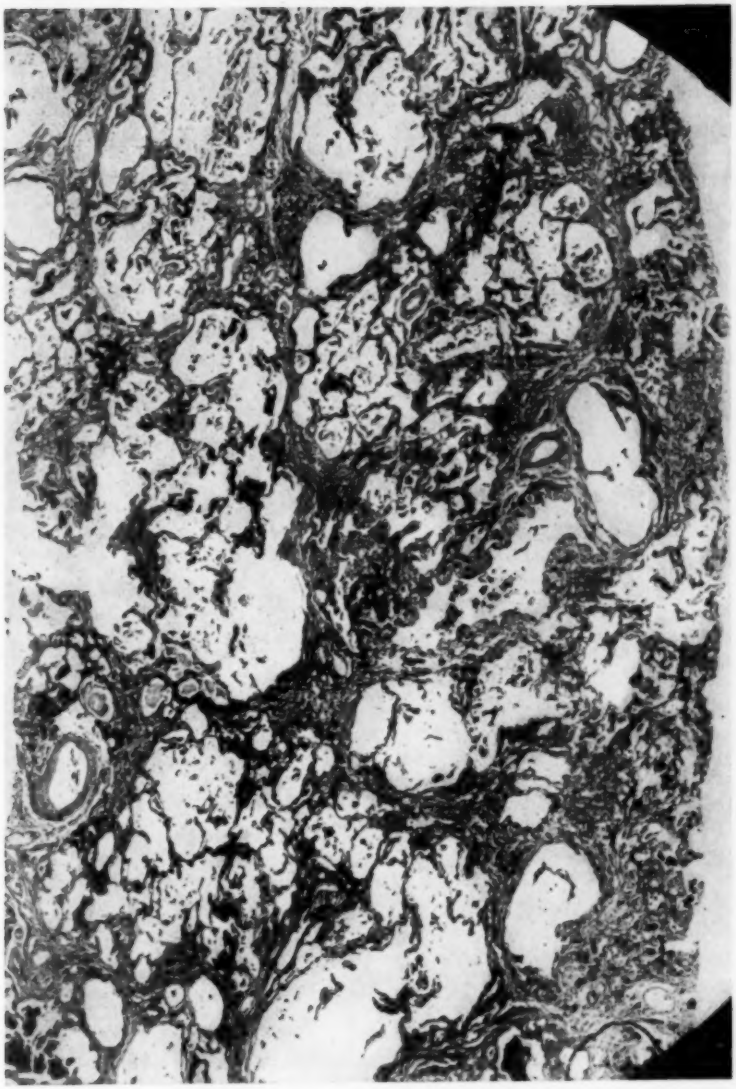

FIG. 2. Photomicrograph of lung, H & E × 20.

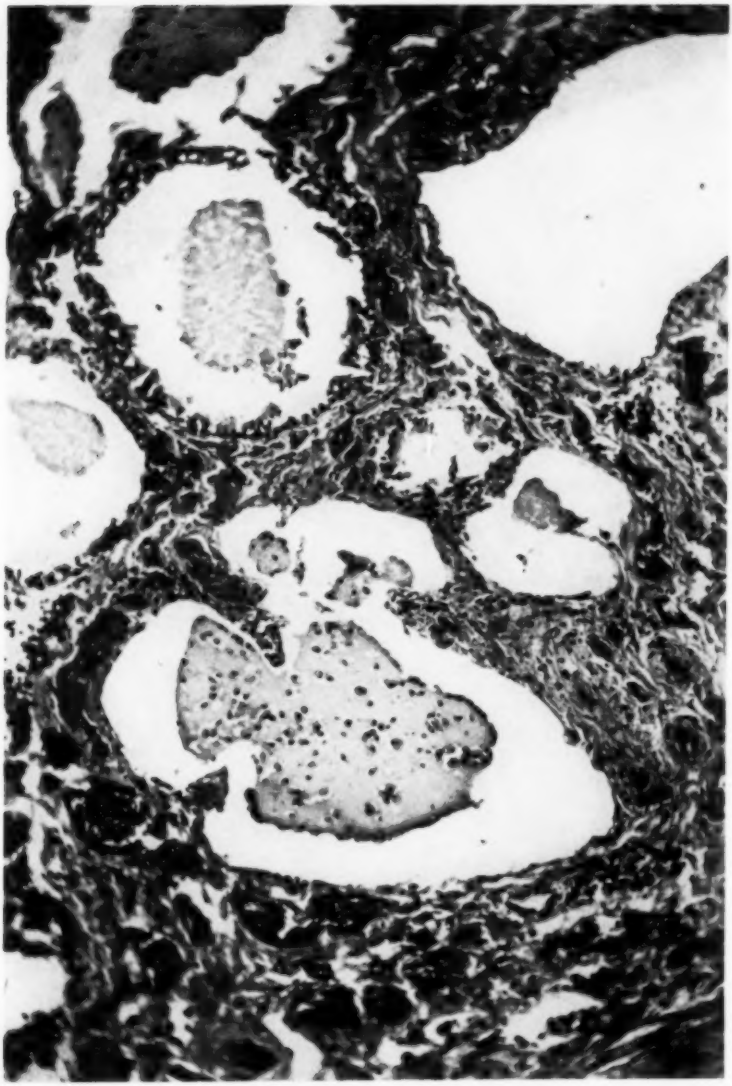

FIG. 3. Photomicrograph of lung. H & E × 150.

moderate number of small congested vessels. There was a sparse mononuclear cell infiltrate in the pericardium.

Multiple sections through the lungs revealed many varying sized cystic spaces, often lined by cuboidal epithelium. Surrounding this lining was a fairly thick fibrous tissue wall. Many of the cystic spaces contained no epithelial lining. Many small alveoli were seen surrounded by dense zones of fibrous tissue. The alveolar septa were diffusely thickened and in places infiltrated with large and small mononuclear cells, plasma cells and a moderate number of polymorphonuclear leukocytes. In other areas the alveoli were dilated and contained fragmented alveolar septa. The bronchioles were dilated and the walls in places infiltrated with lymphocytes and plasma cells. In many of the smaller bronchi, the muscular coat was partially replaced by fibrous tissue. The arteries and arterioles showed moderate sclerosis, the arterioles in particular having thick walls and rather narrow lumens. The pleura was thickened by fibrous tissue and was moderately congested (figures 2 and 3).

Final anatomic diagnosis: scleroderma of skin with involvement of lungs, heart and alimentary tract; diffuse, cystic and compact sclerosis of lung; emphysema of lungs; bronchiolectasis; fibrosis of pleura; focal myocardial fibrosis; hypertrophy and dilatation of right ventricle (cor pulmonale); fibrous atrophy of muscularis of esophagus, stomach and intestines; chronic passive congestion of viscera.

Discussion

In the reports of cases of scleroderma with pulmonary involvement, the changes described were essentially similar. They merely varied in degree. The report by Getzowa [9] is probably the most detailed. In this report the changes were classified into two main types. The first was described as a cystic sclerosis. It was speculated by Getzowa that at first a hyaline fibrotic change took place in the interstitium of the pulmonary parenchyma. Following this, there was an eventual disappearance of the capillaries with a diffuse superimposed fibrosis of the alveolar walls. A dissolution then occurred in many of these alveolar walls which led to the formation of cysts of varying sizes. The second type of change was described by Getzowa as a compact pulmonary sclerosis in which there was no actual dissolution of lung tissue. As a result of the thickening of the alveolar walls, the alveoli were gradually reduced in size and many small alveoli then were contained within zones of compact fibrous tissue. An associated change was a bronchiolar hyperplasia, sometimes assuming an adenoma-like appearance.

Whether or not these were true bronchiolar or bronchial proliferations, or whether it was relative to the contraction of the lung parenchyma, is open to question. The changes found in our case were identical to those described above. However, we could not be sure whether or not all the cystic spaces were primarily the result of tissue dissolution, secondary to the fibrosis and attenuation of the alveolar wall. It was thought by us that probably some of these cystic changes were actually emphysematous bullae developing on an obstructive basis. There was adequate reason for obstruction to occur in the bronchioles, both as a result of the diffuse peribronchiolar fibrosis, and chronic infection associated with the bronchiolectasis; so that the cystic spaces may very well have been the combination of both obstructive emphysema and tissue dissolution.

An additional finding in our case was the presence of a widespread bronchiolectasis. This finding has been noted as well in other reported cases of pulmonary scleroderma. It is interesting to speculate on the mechanism by which this bronchiolectasis may have developed. It is well known in scleroderma that

atrophy and fibrosis are present in the musculature of the alimentary tract. This has been described in great detail by Bevans,[5] and on occasion, it has been the cause of associated clinical manifestations. These changes were also found in our case. However, no clinical manifestations attributable to fibrosis of the gastrointestinal tract were present. A similar change was noted in the musculature of the bronchial tree; i.e., atrophy and fibrosis were present. It is a well known fact that the caliber and tonus of the bronchial tree are to a great extent dependent upon the integrity of its musculo-elastic layer. A necrotic inflammatory process that destroys the musculo-elastic coat may have as its sequela bronchiectasis or bronchiolectasis. One might therefore speculate that the associated bronchiolectasis that is not infrequently found in scleroderma, might be secondary to this fibrosis and atrophy of the muscular coat. However, there are other changes present that might easily have been the cause of the bronchiectasis . . . the diffuse parenchymal fibrosis might have exerted secondary traction on the smaller bronchioles. The fact that the pulmonary parenchyma was distorted and its cleansing mechanism impaired would lay the lung open readily to secondary infection. This secondary infection, suppurative in nature, might also possibly be the cause of the bronchiectasis or bronchiolectasis.

Another point of interest is the occurrence of these cyst-like spaces in the lung parenchyma. The possible mechanisms for their origin have already been mentioned. However, even if some of these cysts are truly the result of obstructive emphysema, the lung as a whole does not resemble the characteristic appearance of a true obstructive emphysema, in that it is not increased in size. If there were a tendency to increase in size, however, it might be to a degree limited by the associated fibrous changes in the pleura that would prevent the lung from expanding.

The functional changes that occur in scleroderma of the lungs can be divided into two fundamental aspects . . . ventilatory disturbances and respiratory disturbances. A fairly definite functional pattern has been noted in scleroderma of the lungs, originally by Matsui.[7] Cournand and Baldwin [10] also have been studying this problem quite extensively for some time. The ventilatory function, i.e., the function of getting air in and out of the lungs, is impaired in scleroderma for a number of anatomic reasons. The involvement of the skin particularly over the thorax impairs to some extent the motions of the chest cage. On occasions, involvement of the diaphragm would impair ventilation. The fibrous contraction of the pleura with resultant compression of the lung is a definite impediment to the expansion of the lung. Finally diffuse peribronchiolar fibrosis with its obstructive emphysema also impairs ventilation. In this case functional studies demonstrated an increase in the residual air indicating impairment of ventilatory function.

The most striking changes, however, were noted in relation to the impairment of respiratory function. The marked thickening of the alveolar walls, the narrowing of the lumina, the thickening of the vascular walls and the obliteration of many of these vessels are adequate to explain the interference with the exchange of gas over the alveolar interface. This was illustrated by a low oxygen content of the arterial blood after exercise. Cournand and Baldwin believe that this respiratory disturbance is the dominant change in scleroderma. Some ventilatory disturbance occurs as well but is not nearly so prominent. It should be noted that these anatomic changes might be present to quite a degree without

producing an obvious clinical picture. Such was the case in one of the patients described by Bevans.[5] In three cases described by Dostrovsky [11] intractable cough was present for many years. Two of these cases were diagnosed during life as pulmonary tuberculosis, although the characteristic skin lesions of scleroderma were present. The anatomic changes in these cases have been described in the report by Getzowa that was referred to above. In the case presented in this report dyspnea was the presenting symptom. However, cough appeared later and persisted.

The heart changes in scleroderma have been described quite comprehensively by Weiss et al.[6] In this case there was pericardial fibrosis, focal myocardial fibrosis with thickening of the myocardial arterioles, subendocardial fibrosis and hypertrophy with dilatation of the right ventricular myocardium. The electrocardiogram showed changes consistent with conduction defects. There were, therefore, several reasons present for the development of a marked cardiopulmonary insufficiency. There was both the combination of myocardial anoxia and pulmonary hypertension.

Some characteristic changes were present in the alimentary tract but these were rather mild and produced no obvious clinical picture.

Summary

A case of scleroderma is presented in which the pulmonary manifestations were prominent, both clinically and at postmortem examination.

Functional disturbances of the cardio-pulmonary system are correlated with the anatomic findings.

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EDITORIAL

THE VERSATILITY OF ADIPOSE TISSUE

FAT is rather firmly associated, in the scientific as well as the lay mind, with a striking absence of activity. As indolence is an accepted attribute of the fat citizen, so tissue fat is regarded as metabolically lazy. But this view is no longer tenable in the light of recent findings. It has become clear that adipose tissue is an organ of many functions. Indeed, the fat is in the metabolic fire.

Adipose tissue is too often regarded merely as a specialized form of connective tissue, although, as long ago as 1870, Toldt stated that the fatty tissue of mammals was a specific organ entirely distinct from the connective tissues. Histologically it is usually thought of as a loose connective tissue of inert cells, more or less stuffed with neutral, inactive fat. Recently obtained data, however, show that adipose tissue develops from special primitive fat cells, and that the cells of this tissue have a specific structure, quite distinct from the fibroblasts of connective tissue. In bulk it is usually considered to be a depot of reserve calories, strategically disposed to subserve the passive functions of an insulator or cushion; or aesthetically arranged to soften the contours of the human form.

These "passive" functions are undeniable and important. Many other active processes involving adipose tissue, however, have lately come to light. As one physiologist has expressed it, "this fat in the depots is not a static dump of material, but is constantly being turned over, even when the total amount is unchanged or increasing." [1]

This very fact that mobilization and deposition go on continually, one outstripping the other according to the supply of materials and the demands of the body, testifies to the unceasing activity of the tissue. Moreover, it has been shown that adipose tissue has a prolific nervous and vascular supply, which is in itself indicative of an active rather than a passive, idle tissue. In Germany, where much of the experimental work on adipose tissue has been performed, evidence has been produced that fat mobilization is dependent on innervation. This nervous control is not mediated, as was once thought, through the vascular system alone, for both parenchyma and vessels have been shown to have an abundant nerve supply. Gersh and Still [2] have recently investigated the blood supply of the fat depots of the rat and found that a high proportion of individual fat cells are in intimate contact with at least one capillary; and that, for metabolic purposes, the capillary bed of fat tissue is comparatively richer than that of muscle. This is an astounding revelation and one again which proclaims the surprisingly great activity of depot fat.

[1] Evans, C. Lovatt: Starling's Principles of Human Physiology, 10th Edition, 1949, Lea & Febiger, Philadelphia, p. 940.

[2] Gersh, I., and Still, M. A.: Blood vessels in fat tissue; relation to problems of gas exchange, J. Exper. Med. **81**: 219, 1945.

The body fat is variably distributed, but the major part of it is divided between the tissues in roughly these proportions: something more than 50 per cent is laid down in the subcutaneous tissue—the panniculus adiposus; about 15 per cent is present in the mesentery; another 10 per cent is in the perirenal depots, and about 5 per cent in the omentum. Another 5 per cent or more is contained in the intermuscular connective tissue; indeed all muscle is interspersed with fat, and the more active the muscle the greater is its ration of interstitial fat. Thus the heart muscle and diaphragm contain a higher proportion of fat than the voluntary skeletal muscles. Here again is a probable indication of the never-ceasing functional importance of tissue fat.

Although fat accounts for about 12 per cent of the average body weight, it has received far less than its due proportion of study. Wells [3] drew attention to this in an excellent review in which he called the adipose tissue "a neglected subject." From the comparatively few investigations which have been devoted to the subject, however, many interesting findings have emerged.

From one point of view it seems most fitting to regard adipose tissue as part of the reticulo-endothelium system. Portis [4] many years ago showed that cells of the omentum are able to form antibodies, and that this ability is correlated with the appearance of aggregates of reticulo-endothelial cells in this organ. These cells show a close histological resemblance to, and probably are identical with primitive adipose tissues before fat storage has begun. Again McCullough [5] has shown that trypan blue is taken up by fat cells, especially after they have become depleted of fat.

Such observations suggest that the cells of adipose tissue, when free of their usual fatty burden, are capable of other activities. But there is also evidence that these cells can and do perform other functions even when in their normal fat-laden state. Thus Bremer [6] clearly showed that vital dyes were stored in the thin protoplasmic ring of distended fat cells.

With the knowledge that adipose tissue is capable of performing reticulo-endothelial functions, it is easier to explain such well known phenomena as the reciprocal tendency of lymphoid and fat tissue to replace each other, as seen especially in the thymus; the obviously close relationship of bone marrow and adipose tissue; and the occasional, apparently vicarious, indulgence of adipose tissue in extra-medullary hematopoiesis.

Apart from reticulo-endothelial functions, there is considerable evidence to show that the fat cell executes several metabolic acts. Not unnaturally most of this metabolic activity is closely related to its function of fat storage. In fact the duty of storing and releasing fat is not itself the passive function

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[4] Portis, B.: Role of omentum of rabbits, dogs, and guinea-pigs in antibody production, J. Infect. Dis. **34**: 159, 1924.

[5] McCullough, A. W.: Evidence of macrophagal origin of adipose cells in white rat as shown by studies on starved animals, J. Morphol. **75**: 193, 1944.

[6] Bremer, J. L.: Protoplasmic film of fat cell, wall of pulmonary alveolus, and renal glomerulus, Anat. Rec. **70**: 263, 1938.

which at first glance it might seem to be. The tissue does not play a submissive rôle and merely acquiesces when the circulation dumps or demands fat; rather it is involved in energetic metabolic changes.

It has been shown repeatedly in the past two decades that adipose tissue itself can carry out desaturation of fatty acids.[7] This observation affords a convenient explanation for the well known fact that the fat laid down in different situations in the body is not all of the same iodine value, the deeper layers being more saturated than the more superficial. Hilditch [8] has proposed an alternative explanation for this variation in iodine value, namely, that all fat is synthesized and transformed in other tissues, and then transported to the depots where the adipose tissue exercises a selective power and chooses the suitably saturated molecule. Whichever of these alternate hypotheses is acceptable, they each presuppose active work on the part of adipose tissue.

Again, it has been recently shown [9] that adipose tissue, incubated in vitro with serum enriched with deuterium oxide, contains fatty acids with stably bound deuterium. Thus it seems securely established that adipose tissue can also synthesize fatty acids.

The presence of glycogen has been repeatedly observed in adipose tissue since 1907. Moreover, it has been demonstrated that its accumulation is always correlated with enhanced fat deposition. This fact led to the supposition that adipose tissue could synthesize fat from carbohydrate,[10] and this possibility was strengthened by the finding that adipose tissue, containing glycogen, exhibited a respiratory quotient exceeding 1.0.[11] It therefore seems probable that glycogen is an intermediary product in the manufacture of fat from carbohydrate by adipose tissue.

Further testimony to the metabolic activity of adipose tissue is afforded by the finding of many enzymes including diastase, phosphatase, and dehydrogenases. It has in fact been noted that adipose tissue is two to three times richer in dehydrogenases of higher fatty acids than is the liver. Mirski [11] has shown that "adipose diastase" is capable of converting glycogen into low polysaccharides; and, on the other hand, that glycogen can be phosphorylated by adipose tissue. There are thus at least two alternative enzymatic processes available in fatty tissue for decomposing glycogen.

And so it is abundantly clear that adipose tissue is an organ of many functions. Not only does it serve as a depot for reserve fat, but it also plays an active part in the processes of deposition and mobilization of that fat. In the process of deposition it not only actively lays down preformed fat, but also makes use of its own ability to manufacture glycogen, and from this to

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[10] Tuerkischer, E., and Wertheimer, E.: Glycogen and adipose tissue, J. Physiol. **100**: 385, 1942.

[11] Mirski, A.: Metabolism of adipose tissue in vitro, Biochem. J. **36**: 232, 1942.

synthesize fatty acids and finally fat. In reverse it is presumably capable of converting fat into glycogen, and finally reducing it, by diastatic or phosphatatic activity, to its constituent low polysaccharides. Besides these functions directly related to the metabolism of fat, it is capable in certain circumstances of assuming the histiocytic faculties of antibody production, blood formation and ingestion of foreign colloidal matter.

An organ so versatile and so active requires a complex but efficient system of regulation. It was stated above that fat mobilization is under nervous control. If the nerves supplying fat tissue are cut and nervous "irritation" is thus eliminated, the affected part accumulates fat. In this connection Hausberger's [12] experiments in mice are classical. He cut the nerve supply to one half of the symmetrical interscapular fat body; within ten hours were observed an influx of glycogen and in its wake an accumulation of fat on the denervated side. This occurred in both the normally fed and starved mouse. As an example of fat loss, on the other hand, as a result of nervous stimulation, the occurrence of facial hemiatrophy from irritation of sympathetic trophic fibers has been cited.

Further evidence of the influence of the autonomic nervous system on fat tissue has been demonstrated in experiments with dogs. From observing the results of isolated section of the sympathetic or parasympathetic supply, it was concluded that sympathetic impulses inhibited fat deposition, while parasympathetic stimuli enhanced it. After complete denervation, both fat deposition and mobilization were reduced and the tissue was found to have a decreased metabolic rate. The obesity which is part of hypothalamic syndromes is further evidence of nervous influence on fat accumulation; and a similar adiposity can constantly be produced in rats by experimental lesions to the hypothalamus.[13, 14] Adipose tissue, in fact, seems to possess what Wertheimer and Shapiro [15] call "a certain 'tonus' "—the result of a constant, reciprocal autonomic innervation. Imbalance in one direction will lead to obesity in the affected part, while leanness will result if the balance is upset in the other direction.

But this is not the whole story of tissue fat regulation. As would be expected there is much evidence to suggest that the endocrine system also plays an important part in its control. The injection of anterior pituitary extracts into fasting mice has been shown to produce fatty livers through excessive mobilization of depot fat and its migration to the liver.[16, 17] More recently it has also been demonstrated in both rats and man that lactogenic

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hormone reduces the fat content of adipose tissue.[18] This action may, of course, be directly related to the normal manufacture of milk.

The adrenal cortex also has a say in the metabolism of depot fat. Thus, in adrenalectomized animals, fat deposition, both in the liver and the depots, is inhibited. This is accompanied by a reduction in glycogen deposition also, which suggests that conversion of carbohydrate to fat is influenced.

And insulin also plays its part, for it has been shown to prevent the development of fatty livers in pancreatic and phloridzin diabetes, and in fasting animals subjected to injections of anterior pituitary extracts. This has frequently been assumed to represent an indirect action through the influence of insulin on carbohydrate metabolism. But Wertheimer [19] has shown that insulin injection causes glycogen to appear in the adipose tissue of the normally fed rat, and he has concluded that insulin exerts a direct effect on glycogen synthesis in adipose tissue. In this connection it has been found that alloxan diabetic rats are unable to store glycogen in their adipose tissue, but insulin completely reverses this inability.[20] Since adipose tissue participates in fat synthesis in the body,[9] and since insulin is essential for normal glycogen and fat deposition in adipose tissue, an obstruction to the metabolism of this tissue may clearly be an important aspect of the pathophysiology of diabetes.

The importance to the internist of these basic studies is the light that they may shed on the underlying mechanisms of obesity. It is generally thought and taught that, except in rare cases of gross endocrinopathy, the cause of obesity is a simple imbalance between calorie intake and exercise. Important as such imbalance undoubtedly is, it is too sweeping to state that "a plethora of calories is the only explanation of obesity." [21] It is clear that among other causes an imbalance in the normal "tonic" innervation of adipose tissue may be responsible, just as an imbalance in reciprocal autonomic innervation has been suggested in the pathogenesis of other diseases such as asthma, achalasia of the cardia, Hirschsprung's disease, and others. Perhaps it is not too far-fetched to suggest that part of the weight-reducing action of amphetamine and allied compounds may be explained on the basis of a sympathomimetic action on adipose tissue, rather than based entirely on their anorexigenic effect. Again, the weight loss in hyperthyroidism may perhaps be related to the enhanced sympathetic activity in this disease, leading to direct "irritation" of adipose tissue, and not be entirely the result of increased metabolism per se. At least it is to be hoped that recent advances in our knowledge of the physiology of adipose tissue will inspire more fundamental research in this field, and, at the same time, encourage in the practicing physician a more thoughtful approach to the vexing problem of obesity.

H. J. L. M.

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REVIEWS

The Adrenal Gland. By FRANK A. HARTMAN, Ph.D., and KATHARINE A. BROWNELL, Ph.D. 581 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1949. Price, $12.00.

It would be difficult indeed to find another book which covers in the same compass the material on the adrenal gland presented here. Nothing important concerning the anatomy, physiology, embryology, pharmacology, chemistry or pathology is neglected. In addition there is an enlightening and comprehensive discussion of clinical implications. In the preface the authors modestly state that they have attempted to cover all phases of the subject. In the opinion of this reviewer these attempts have been crowned with success. It is true, as they recognize, that the functional side is given more stress, but other aspects of the adrenal gland are far from neglected. Every physician who is at all interested in trying to correlate what he sees in his practice with some of the recent findings of the endocrinologists should add this book to his library. The adrenal, today, is coming to be considered as one of the prime integrating organs of the body, and knowledge of its functions is necessary if one is to grasp the meaning of homeostasis. The recent revelation of the importance of certain adrenal cortical steroids in the treatment of arthritis only adds to the necessity for learning still more about this gland.

The organization of the book is excellent. The first hundred pages deal with the comparative and developmental anatomy of the adrenal as well as its histology. Here the information, brought together from widely scattered sources, will be of great value to the student and the research worker. A discussion of the chemistry of the chromaffin and cortical tissues comes next, followed by an excellent account of the physiology of the adrenal medulla, including a consideration of the pharmacology of epinephrine or adrenalin. The remaining two-thirds of the book are devoted to summarizing our current knowledge of the adrenal cortex, including its pathology and its relation to other glands of internal secretion. Each chapter ends with a summary which underlines all the important material which the chapter contains. The bibliography lists well over 3,000 titles and it is difficult to imagine any paper in any accessible journal which has been omitted. The inclusion of an authors' index will make the book extremely useful in guiding the reader to a review of the papers mentioned in the bibliography. The subject index is well done. In fact, the physical organization of the book makes it a useful tool both to the experimentalist and the clinician. It can well stand as a model of its kind.

The general tone of the book is one of dispassionate objectivity and the authors take up no cudgels for any particular theory of adrenal function. They are content to let the facts speak for themselves, and any intelligent reader with a good physiological background should be able to draw his own conclusions. At the same time, the book is no mere catalog of data.

It is, of course, always possible in a book of this sort to find minor points on which opinions might differ. This reviewer takes some exception to the space devoted to the adrenal medulla and its relationship to the sympathetic nervous system. Possibly in a strict sense this subject lies outside the scope of the book, but it is one which must be discussed if the true significance of the adrenal medulla is to be understood at all. Also, the discussion concerning the possibility of there being two types of adrenalin, one excitatory and the other inhibitory (at least insofar as action on the smooth muscles of the arterioles is concerned) is not too strong. The recent demonstration of the existence of nor-adrenalin as a normal constituent of adrenalin extracted from the adrenal medulla now makes it almost certain that the gland secretes

a vaso-dilator as well as a vaso-constrictor hormone. This work, however, appeared too late to be included in this book.

The book brings out very well how such basic bodily functions as sexual activity, carbohydrate metabolism, water and salt balance, and resistance to stress are all in some way related to the adrenal cortex. Recent work on the relationship between the adrenal cortex and the pituitary is well handled and the actual rôle of adrenocorticotrophic hormone in governing cortical function is well covered.

To the clinician the three chapters on adrenal insufficiencies, together with the two chapters on hyperactivity, will probably be the most interesting. Addison's disease is given thorough treatment, and the discussion of the adreno-genital syndrome is one of the best in the literature. Certain cautious suggestions are made concerning the use of cortical extracts in various clinical states, but the authors stress the experimental nature of the work. Considering some of the most recent and most startling developments in the clinical application of cortical steroids, such restraint seems overly conservative. However, one need only recall the high hope held in certain quarters concerning the use of cortical extracts in the treatment of traumatic shock, and the subsequent disappointment of the clinical trials, to understand the authors' wariness. Even though the close relationship between the adrenal cortex and the stress states has been amply demonstrated experimentally, it is perhaps just as well to exercise some reserve in these matters when applying the information to clinical situations.

DIETRICH C. SMITH

Evaluation of Chemotherapeutic Agents. Edited by COLIN M. MACLEOD, M.D. 205 pages; 15.5 × 23.5 cm. Columbia University Press, New York. 1949. Price, $4.00.

This book dealing with the methods of evaluation of chemotherapeutic agents is the second in a series of symposia of the Section of Microbiology of the New York Academy of Medicine. Ably organized and edited by Dr. MacLeod contributions are made by leaders in the field of antimicrobial therapy. Basic fundamental information pertaining to blood and tissue concentration of synthetic and antibiotic compounds, their absorption, distribution, elimination and methods of activity are discussed. Theories of microbial resistance in host-parasite relationship to chemotherapy are elucidated. The book describes the many factors involved in the chemoprophylaxis and chemotherapy of infections of meningococcal, protozoal, rickettsial and viral origin. Detailed procedure is not a function of this symposia, although each author has judiciously selected bibliographical references designed to guide the investigator. Two chapters devoted to experimental and clinical evaluation of chemotherapeutic agents in cancer introduce the reader to certain hormonal and cytotoxic agents held potentially useful in this field.

The book presents authoritative scientific data and concepts by well-known authorities, which is of inestimable value to microbiologists, laboratory and clinical investigators and students interested in the fundamental approach to anti-microbial therapy.

T. E. W.

Diagnosis of Viral and Rickettsial Infections. Edited by FRANK L. HORSFALL, JR. 153 pages; 11.5 × 23.5 cm. Columbia University Press, New York. 1949. Price, $3.75.

This symposium provides for the reader the acceptable methods in use for diagnosis of disease caused by viral and rickettsial agents. Each chapter is written by a well-known authority who summarizes his critical judgment as to the indications for the use of applicable laboratory procedures, their practicability, and the interpretations

that should be made of the results. The essential clinical features of each disease are briefly presented. Well written, well documented, with extensive references to the literature the book provides basic and dependable information of the greatest value both to the clinician and to the laboratory investigator.

T. E. W.

The Acute Bacterial Diseases: Their Diagnosis and Treatment. By HARRY F. DOWLING, M.D., F.A.C.P. 465 pages; 15.5 × 24 cm. W. B. Saunders and Company, Philadelphia. 1948. Price, $6.50.

The author has admirably succeeded in presenting a practical guide for physicians and interested students who deal with acute bacterial infections. General factors in the diagnosis of infectious diseases are considered, various diagnostic procedures are emphasized, tables are presented which simplify differential diagnoses in common infections. Supportive measures are given adequate consideration. Of particular value are the chapters dealing with serums, sulfonamides, penicillin and streptomycin and their employment in the treatment of the bacterial diseases. There are helpful illustrative diagrams which stress (1) clinical and laboratory procedures needed before institution of specific therapy, (2) methods of administration of the specific agent and (3) helpful points pertaining to supportive measures, and to laboratory procedures essential as a guide during therapy.

Part II of the book is devoted to a discussion of individual diseases, classified according to the etiologic agent responsible for them. Dr. Dowling's descriptions of disease are excellent. He emphasizes the practical objectives of diagnosis and treatment. Sufficient details pertaining to epidemiology, pathogenesis and pathology are given. Information regarding the technics of laboratory tests is limited. There are many excellent illustrations and the references appended to each chapter constitute another good feature. Though the rapid advances being made in our knowledge of the acute bacterial diseases will necessitate frequent new editions, the present volume will retain its position as a valuable and helpful summary of the clinical aspects of this group of infections and a guide to their diagnosis and treatment.

T. E. W.

Starling's Principles of Human Physiology. 10th Ed. By C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D., Jodrell Professor of Physiology in University College, London. 1193 pages; 15.5 × 24.5 cm. Lea and Febiger, Philadelphia. 1949. Price, $10.00.

This is the sixth revision of Starling's text by Professor Evans, and it exceeds its predecessor by 38 pages and 60 illustrations. Dr. Hartridge, who is director of the Vision Research Unit of the Medical Research Council of Great Britain, has again revised the chapters on the Special Senses.

The book has many excellent features. It is for the most part beautifully written in a pungent, direct style which is explicit and easy to follow. Most of the 693 illustrations are of a high standard. On the whole the text is up-to-date, and such new developments as vitamin B_{12} and the recent additions to the sum of coagulation factors in the blood are briefly but adequately covered.

On the other hand it is surprising to find no reference to the recent concept of hypersplenism, and the related advances in splenic physiology which have lately exalted the spleen to the status of an endocrine organ. And there appears to be no excuse for perpetuating the antiquated and inaccurate description of electrocardiographic changes in bundle branch block under the heading "The Human Electrocardiogram." The description as it stands may be all right for the dog (as Wilson pointed out as long ago as 1943), but under the present heading radical revision of

this description is required. Again the statement concerning the relative capacity of ventricles and auricles does not coincide with Hochrein's widely accepted work on the subject.

It is a pity that so much of the interesting subject matter has to be relegated to a print of diminutive size which is no pleasure to read.

All in all this is a standard and well produced work on scientific physiology. From the internist's point of view, however, it is neither the most readable nor the most valuable text, as its approach to the subject of physiology is emphatically basic and not applied. It remains an excellent textbook for the student of physiology.

H. J. L. M.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Acute Appendicitis and Its Complications. By FREDERICK FITZHERBERT BOYCE, M.D., Diplomate of the American Board of Surgery, etc. 487 pages; 23.5 × 15.5 cm. 1949. Oxford University Press, New York. Price, $8.75.

Allergy in Relation to Otolaryngology. By FRENCH K. HANSEL, M.D., M.S., F.A.C.A., Editor-in-Chief, Annals of Allergy, etc. Panel Discussion: HAROLD A. ABRAMSON, M.D., KENNETH L. CRAFT, M.D., JEROME GLASER, M.D., IRVING B. GOLDMAN, M.D., M. MARTYN KAFKA, M.D., GRANVILLE F. KNIGHT, M.D., HUGH A. KUHN, M.D., JOHN H. MITCHELL, M.D., and WALTER E. OWEN, M.D. 77 pages; 20 × 14 cm. 1949. An official publication of the American College of Allergists. Bruce Publishing Company, Saint Paul and Minneapolis. Price, $2.50.

An Atlas of the Blood and Bone Marrow. By R. PHILIP CUSTER, M.D., Director, Laboratories of the Presbyterian Hospital in Philadelphia, etc. 321 pages; 29.5 × 20 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $15.00.

The Clinical Examination of the Nervous System. 9th ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, etc. 459 pages; 19 × 13 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $5.00.

The Diagnosis and Treatment of Adrenal Insufficiency. By GEORGE W. THORN, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, etc.; with the collaboration of PETER H. FORSHAM, M.D., M.A. (Cantab.), Assistant in Medicine, Harvard Medical School, etc., and KENDALL EMERSON, JR., M.D., Associate in Medicine, Harvard Medical School, etc. 171 pages; 22.5 × 14.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $5.50.

Diseases of the Heart. By CHARLES K. FRIEDBERG, M.D., Associate Physician, Mount Sinai Hospital, New York, etc. 1081 pages; 25 × 17 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $11.50.

Dr. Tom Brown: Memories. By JEANNIE ALBERT BROWN. 103 pages; 22.5 × 14.5 cm. 1949. Richard R. Smith, New York. Price, $2.50.

Ecology of Health: The New York Academy of Medicine Institute on Public Health, 1947. Edited by E. H. L. CORWIN, Ph.D. 196 pages; 21.5 × 14 cm. 1949. The Commonwealth Fund, New York. Price, $2.50.

Normal Values in Clinical Medicine. By F. WILLIAM SUNDERMAN, M.D., Ph.D., Professor of Experimental Medicine and Clinical Pathology, University of Texas Postgraduate School of Medicine, etc., and FREDERICK BOERNER, V.M.D., Late Associate Professor of Clinical Bacteriology, Graduate School of Medicine, University of Pennsylvania, etc. 845 pages; 26 × 17.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $14.00.

Nutritional Data (formerly "Nutritional Charts"). By HAROLD A. WOOSTER, JR., and FRED C. BLANCK. 114 pages; 23 × 19 cm. (plastic bound, loose-leaf). 1949. H. J. Heinz Company, Pittsburgh. Gratis.

Pavlov: A Biography. By B. P. BABKIN. 365 pages; 21.5 × 14 cm. 1949. The University of Chicago Press, Chicago. Price, $6.00.

Het Rubella-Probleem in Het Licht Van Nederlandse Ervaringen. By DR. A. ELISABETH H. M. KAMERBEEK. 212 pages; 24 × 16 cm. (paper-bound). 1949. H. E. Stenfert Kroese's Uitgevers-Mij. N.V., Leiden. Price, f. 7.—

Selective Partial Ablation of the Frontal Cortex: A Correlative Study of Its Effects on Human Psychotic Subjects. THE COLUMBIA-GREYSTONE ASSOCIATES, FRED A. METTLER, M.D., Ph.D., Editor. 517 pages; 26 × 18 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Stern's Applied Dietetics: The Planning and Teaching of Normal and Therapeutic Diets—3d ed. Revised by HELEN ROSENTHAL, B.S., Chief of Frances Stern Food Clinic, The Boston Dispensary, etc.; PEARL C. BAKER, B.S., Former Associate, Frances Stern Food Clinic, The Boston Dispensary, and WILMA A. MCVEY, M.D., Assistant in Medicine, Tufts College Medical School. 293 pages; 26 × 17.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $5.00.

The Thyroid Hormones and Their Action. 2nd ed. By G. MANSFELD, M.D., Professor of Physiology, University of Budapest; translated by ERWIN PULAY, M.D. 157 pages; 25 × 16 cm. 1949. Frederick Muller, Ltd., London. Price, 24′ net.

X-Ray Treatment: Its Origin, Birth and Early History. By ÉMIL H. GRUBBÉ, B.S., M.D., F.A.C.P., Charter Member and Emeritus Member of the Radiological Society of North America, etc. 153 pages; 23.5 × 15.5 cm. 1949. The Bruce Publishing Company, Saint Paul and Minneapolis. Price, $3.00.

COLLEGE NEWS NOTES

31ST ANNUAL SESSION, AMERICAN COLLEGE OF PHYSICIANS BOSTON, APRIL 17–21, 1950

The program of the 31st Annual Session of the American College of Physicians will be published in the February issue of this journal. A separate program will be printed and distributed to each member of the College, to every candidate for membership and to those physicians who have requested copies.

Hotel reservation forms will accompany the individual program.

The Technical Exhibit will be the largest and most interesting one ever held in connection with the Annual Session of the College. There are 124 booths and 99 separate exhibitors. A feature of the Technical Exhibit of the American College of Physicians is the restriction of all exhibits to the field of Internal Medicine and its allied specialties, with elimination of all exhibits that are irrelevant to the practice of medicine. Physicians will find assembled in this exhibit the most worthy of the manufacturers of medical supplies, pharmaceuticals, publishers of medical books, and the exhibit will be a contribution to the interest and success of the meeting.

Arrangements have been concluded through Mr. Leon V. Arnold, Travel Consultant, 36 Washington Square West, New York 11, N. Y., for a post-convention cruise from New York to Bermuda. There are no interesting tours available in New England at so early a date in the Spring and thus, at the request of some who were unable to take the Bermuda cruise following the 1949 New York Session, arrangements were concluded to accommodate another party from the College this year. Members may proceed to New York over Friday night or even Saturday morning, following the Boston meeting. Sailing on the *Queen of Bermuda* will be at 3:00 p.m. Saturday, April 22, and the party will return to New York, leaving Bermuda at 3:00 p.m., April 26, and arriving in New York at 9:00 a.m., April 28. For full information, application for staterooms, etc., inquiry should be sent directly to Mr. Arnold.

New Jersey Regional Meeting

New Jersey members of the American College of Physicians held their annual Regional Meeting at Newark, N. J., on November 30, 1949, under the Governorship of Dr. George H. Lathrope of Newark. Dr. Johannes F. Pessel of Trenton was the Chairman of the Program Committee, and Dr. Edward C. Klein, Jr., of Newark, was Chairman of the Committee on Arrangements. The scientific session was held at the Academy of Medicine of Northern New Jersey, and the program was as follows:

Moderator

Jerome G. Kaufman, M.D., F.A.C.P., Newark

Modern Trends in Cardiology.

Jerome G. Kaufman, M.D., F.A.C.P., President, New Jersey Heart Association.

The Use of the Cation Exchanges in Chronic Cardiac Decompensation.

Henry C. Crossfield, M.D., F.A.C.P., East Orange.

Heart Disease and Myxedema.

Thomas J. White, M.D., F.A.C.P., Jersey City.

Myocarditis.

William G. Bernhard, M.D., F.A.C.P., Newark.

Moderator

JOHN E. LEACH, M.D., F.A.C.P., Paterson

The Use of Compound E, ACTH Adrenal Cortical Hormones.
C. P. SILIRIE, M.D. (by invitation), Rahway.
The Purpuras.
CHARLES H. LANDSHOF, M.D., F.A.C.P., Jersey City.
Diverticulosis and Diverticulitis.
REUBEN L. SHARP, M.D. (Associate), Camden.
Psychosomatics.
EDWARD A. STRECKER, M.D., F.A.C.P., Philadelphia, Pa.

In the evening a social hour and reception was held at the Downtown Club, followed by dinner, at which Dr. Lathrope was the Toastmaster. Some of the special guests included Dr. George Morris Piersol, Philadelphia, Secretary General of the College, Dr. Edward L. Bortz, Philadelphia, member of the Board of Regents, Dr. William D. Stroud, Philadelphia, Treasurer of the College, Dr. Thomas M. McMillan, Philadelphia, College Governor for Eastern Pennsylvania, Dr. Lemuel C. McGee, Wilmington, College Governor for Delaware, Dr. Asa L. Lincoln, New York, College Governor for Eastern New York, and Mr. Edward R. Loveland, Philadelphia, Executive Secretary of the College. The chief speakers were Dr. Reginald Fitz, Boston, President of the College, and Judge William H. Speer, General Counsel, Retired, Public Service Corporation of New Jersey. The addresses were especially appropriate, both instructive and entertaining. There were in attendance approximately 175 physicians. During the course of the evening ceremonies, Dr. Edward C. Klein, Jr., presented to Governor Lathrope on behalf of the Fellows and Associates of the State a very fine leather travel clock embossed with the Seal of the College and Dr. Lathrope's name.

KENTUCKY REGIONAL MEETING

The annual Regional Meeting of the College for the State of Kentucky was held at Louisville, December 3, 1949, under the Governorship of Dr. J. Murray Kinsman, F.A.C.P. Dr. Carlos A. Fish (Associate) was Chairman of Arrangements and Dr. Lawrence T. Minish, Jr., F.A.C.P., was Chairman of the Program Committee. The program was as follows:

Presiding

LAWRENCE T. MINISH, JR., M.D., F.A.C.P., *Program Chairman*

Treatment of Amoebiasis with Atabrine.
LT. COL. RYLE A. RADKE, SR., M.D. (Associate), Fort Knox, Kentucky.
Chronic Intestinal Disorders, Infectious and Parasitic.
W. REEVE HANSEN, M.D. (by invitation), Nichols V. A. Hospital, Louisville, Kentucky.
Ulcerative Colitis.
JOHN D. TRAWICK, JR., M.D. (Associate), Louisville, Kentucky.
Observations on the Huggin's Thermocoagulation Test.
MALCOLM L. BARNES, M.D. (Associate), Louisville, Kentucky.
Observations on Circulation Time Determinations. Demonstration.
HERBERT L. CLAY, M.D. (Associate), and JACK CHUMLEY, M.D. (by invitation), Louisville, Kentucky.
Cardiac Output Studies.
WALTER S. COE, M.D. (by invitation), and MAURICE M. BEST, M.D. (by invitation), University of Louisville School of Medicine, Louisville, Kentucky.

There was a reception and informal banquet in the evening at the Pendennis Club. Dr. William S. Middleton, F.A.C.P., President-Elect of the College and Dean of the University of Wisconsin School of Medicine, was the chief speaker. As always, this was a most successful and enjoyable meeting, attended by nearly all the Kentucky members and many guests.

North Carolina Regional Meeting

The annual Regional Meeting of the College for North Carolina was held at Winston-Salem, N. C., Friday, December 9, 1949, under the Governorship of Dr. Paul F. Whitaker, F.A.C.P., Kinston. Dr. Edward S. Orgain, F.A.C.P., Durham, was Chairman of the Program Committee and Dr. George Harrell, F.A.C.P., Winston-Salem, was Chairman of the Committee on Arrangements. The meeting was held at the Bowman Gray School of Medicine and the program was as follows:

The Use of Radioactive Isotopes in the Study of Liver Disease.
David Cayer, M.D., F.A.C.P.

Practical Information Which Has Been Derived from Special Studies of the Circulation.
John Hickam, M.D. (Associate).

Hypertension and Toxemia of Pregnancy—Problems of Mutual Interest to the Internist and to the Obstetrician.
Walter L. Thomas, M.D. (by invitation).

Newer Concepts of Carbohydrate Metabolism and Their Bearing on the Problem of Diabetes Mellitus.
Charles W. Styron, M.D. (Associate).

Clinicopathologic Conference.
Richard Z. Query, Jr., M.D., F.A.C.P., and Paul Kimmelstiel, M.D. (by invitation).

In the evening, a reception and dinner were held at the Old Town Club. Dr. Whitaker was Toastmaster; Dr. Marshall Brucer delivered the address, "Radioactive Isotopes in Medicine."

Southeastern Regional Meeting

The annual Regional Meeting of the Southeastern States, including Alabama, Florida, Georgia, South Carolina, and Cuba, was held at the Medical College of Alabama, Birmingham, Ala., December 10, 1949, under the general chairmanship of Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, and with the coöperation of the Governors for the individual states and Cuba participating. The program was as follows:

Morning Session

Edgar G. Givhan, M.D., F.A.C.P., Birmingham, *Presiding*

The Clinical Features and Treatment of "The Shock Kidney."
Duward O. Wright, M.D., F.A.C.P., Medical Director, American Cast Iron Pipe Company, Birmingham, Ala.

The Pathology of "The Shock Kidney."
Joseph F. A. McManus, M.D. (by invitation), Associate Professor of Pathology, Medical College of Alabama, Birmingham, Ala.

The Expanding Problem of Matching Blood for Transfusion.
Joseph A. Cunningham, M.D. (by invitation), Assistant Professor of Pathology, Medical College of Alabama, Birmingham, Ala.

Clinical Disorders of the Neurohypophysis.
THOMAS P. FINDLEY, M.D., F.A.C.P., Head of the Department of Medicine, Ochsner Clinic, New Orleans, La.

AFTERNOON SESSION

JAMES B. MCLESTER, M.D., F.A.C.P., Birmingham, *Presiding*

Pulmonary Manifestations of Congestive Heart Failure.
JAMES WARREN, M.D. (by invitation), Professor of Physiology, Emory University School of Medicine, Atlanta, Ga.
The Importance of the Cervical Spine to the Internist.
A. IZARD JOSEY, M.D., F.A.C.P., Columbia, S. C.
The Psychological Treatment of Tuberculosis.
WALTER M. BARTLETT, M.D., F.A.C.P., Area Section Chief of Internal Medicine, Veterans Administration, Atlanta, Ga.
The Diagnosis and Treatment of Esophageal Hiatus Hernia.
CHARLES DONALD, M.D. (by invitation), Assistant Professor of Surgery (Division of Thoracic Surgery), Medical College of Alabama, Birmingham, Ala.

In the evening, a reception and banquet were held at the Thomas Jefferson Hotel. Dr. Reginald Fitz, F.A.C.P., Boston, President of the College, was the speaker. Dr. E. G. Givhan, Jr., F.A.C.P., Birmingham, was the Chairman of the Committee on Arrangements for the entire meeting.

OTHER PENDING REGIONAL MEETINGS

Eastern Pennsylvania will hold its annual Regional Meeting at Philadelphia on January 20, 1950, under the Governorship of Dr. Thomas M. McMillan, F.A.C.P. Dr. Howard B. Sprague, F.A.C.P., Boston, will be the invited guest speaker at the banquet.

The first annual Regional Meeting for the Provinces of Manitoba and Saskatchewan will be held at Winnipeg, Manitoba, February 10, 1950, under the Governorship of Dr. C. H. A. Walton, F.A.C.P.

The annual Nebraska Regional Meeting will be held at Lincoln, Nebraska, February 11, 1950, under the Governorship of Dr. Joseph D. McCarthy, F.A.C.P. Dr. William S. Middleton, F.A.C.P., President-Elect of the College, will be the chief guest speaker and will address the banquet in the evening.

The annual Colorado Regional Meeting will be held at Denver, February 21, 1950, under the Governorship of Dr. Ward Darley, F.A.C.P., and the general chairmanship of Dr. Louis Faust, F.A.C.P., both of Denver. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the College will be the chief guest speaker.

The Virginia Annual Regional Meeting is scheduled for February 22, in Richmond, under the Governorship of Dr. J. Edwin Wood, Jr., F.A.C.P., Charlottesville, Va. Dr. J. Franklin Waddill, of Norfolk, is the Secretary of the Virginia chapter. President Reginald Fitz, of Boston, will be the guest speaker.

The Kansas Regional Meeting is scheduled for Topeka, Friday, March 17, 1950, under the Governorship of Dr. William C. Menninger, F.A.C.P. Invitations are being extended, through the respective College Governors, to the members in Colorado, Nebraska, Missouri and Oklahoma to attend this meeting. Dr. Hugh J. Morgan, F.A.C.P., Regent and former President of the College, will be the chief guest speaker.

A.C.P. Postgraduate Courses, Spring and Summer, 1950

CLINICAL ALLERGY—Roosevelt Hospital, New York, N. Y.; Robert A. Cooke, M.D., F.A.C.P., Director; two weeks, February 6–18, 1950. Fees: A.C.P. Members, $120.00; Non-members, $240.00. This will be chiefly a clinical course in Allergy and will be limited to 8 registrants.

DISEASES OF THE BLOOD VESSELS—Cornell University Medical College, New York, N. Y.; Irving S. Wright, M.D., F.A.C.P., Director; one week, March 13–18, 1950. Fees: A.C.P. Members, $30.00; Non-members, $60.00. This is a new course on the College program and should be one of great value.

CARDIOLOGY—Michael Reese Hospital, Chicago, Ill.; Louis N. Katz, M.D., F.A.C.P., Director; one week, March 20–25, 1950. Fees: A.C.P. Members, $30.00; Non-members, $60.00. This also is a new course on the College schedule. The Director is widely known for the courses he has given and his work in the field of Cardiology. It is predicted that it will be a popular course and that few, if any, non-members can be accommodated.

ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION—Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; one week, May 8–13, 1950. Fees: A.C.P. Members, $60.00; Non-members, $120.00. This course is regularly on the College schedule. It is designed to acquaint the student of electrocardiography with modern theory and its clinical application. It is expected that the registration will be limited to 25 physicians.

INTERNAL MEDICINE—University of California Medical School, San Francisco, Calif.; Stacy R. Mettier, M.D., F.A.C.P., Director; one week, June 19–24, 1950 (the week preceding the annual meeting of the American Medical Association at San Francisco). Fees: A.C.P. Members, $30.00; Non-members, $60.00. A similar course was organized and directed by Dr. Mettier for the College preceding the last annual meeting of the American Medical Association in San Francisco. It was a most successful course and the registration was large. The course will be still further improved and extended this year, and presents an opportunity to members of the College who will be attending the annual meeting of the American Medical Association to attend an advanced course in Internal Medicine on the West Coast.

ENDOCRINOLOGY—University of Illinois College of Medicine, Chicago, Ill.; Willard O. Thompson, M.D., F.A.C.P., Director; one week, date yet to be determined. Fees: A.C.P. Members, $30.00; Non-members, $60.00. This course has been given on several previous occasions with signal success and an exceptionally large registration.

CLINICAL ASPECTS OF MALNUTRITION—Hospital de Enfermedades de la Nutrición, Mexico, D. F.; Salvador Zubiran, M.D., F.A.C.P., Director; two weeks, August 14–26, 1950. Fees: A.C.P. Members, $60.00; Non-members, $120.00. This is an entirely new course on the College program. There is probably no institution and group of teachers better qualified to give a postgraduate course in the field of nutrition than those selected for this course. A combination of clinical and didactic instruction will be given daily from 9:00 a.m. to 1:00 p.m. Afternoons will be open for organized sightseeing trips in Old Mexico. This course provides an opportunity not only for postgraduate instruction but for a most interesting vacation.

In the preceding issue of this journal the College tentatively announced three additional courses—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, at Duke University School of Medicine, Durham, N. C.; Dr. Eugene A. Stead, Jr., F.A.C.P., Director; MECHANISMS OF DISEASE, at the Peter Bent Brigham Hospital, Boston, Mass.; Dr. George W. Thorn, F.A.C.P., Director; and PHYSIOLOGICAL BASIS OF PSYCHOSOMATIC MEDICINE, at the Neurological Institute, New York, N. Y.; Dr. Harold G. Wolff, F.A.C.P., Director. Due to extenuating circumstances, it now seems improbable that these courses can be set up for

the Spring of 1950, but will be delayed until some future time. The Advisory Committee on Postgraduate Courses is arranging other courses to take the place of these delayed courses and will include suitable announcements in the Postgraduate Bulletin to be published during January.

For all information, registration forms and directions, write E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

New A.C.P. Life Members

Dr. James C. Metts, F.A.C.P., Savannah, Ga., and Dr. James F. McFadden, F.A.C.P., St. Louis, Mo., became Life Members of the American College of Physicians during December.

This is the season when an increasing number of Fellows should be considering Life Membership. The College plan is an equitable and practical arrangement by which a member may pay his dues during his productive years and while his income is greatest, thus avoiding the burden of dues later in life. Life Membership offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. Life Membership is accorded to Fellows or Masters up to 50 years of age by the payment of $300.00, in addition to the initiation fee paid at the time of election. Over 50 years of age to 60 years of age, a Fellow or Master shall pay an amount equivalent to the total amount of dues he would ordinarily pay from his present age to the age of 65. From the age of 60 forward, the minimum Life Membership fee is $100.00.

The Life Membership Fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions and to the Annals of Internal Medicine, etc. Each Life Member receives a framed Certificate, and his name is inscribed on the Life Member Scroll at the College Headquarters. Life Members are active members for life. All Life Membership fees are deposited in the permanent Endowment Fund of the College and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns.

Candidates for Membership

The Committee on Credentials of the American College of Physicians will meet on March 19, at Philadelphia; on April 15, at Boston; and during November, at Philadelphia, 1950. The By-Laws provide that proposals of new members must be filed in the Executive Office of the College at least 60 days in advance of action. Therefore, proposals of new members for action at the Annual Session of the College at Boston in April must be submitted no later than February 15, 1950.

Coming Examinations of Certifying Boards

(1) American Board of Internal Medicine; William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison, Wis. Oral Examinations—Chicago, Ill., February 8, 9, 10, 1950; Boston, Mass., April 13, 14, 15, 1950 (the week preceding the Annual Session of the American College of Physicians at Boston); San Francisco, Calif., June 21, 22, 23, 1950 (the week preceding the annual meeting of the American Medical Association at San Francisco).

Oral examinations in the subspecialties of Allergy, Cardiovascular Diseases, Gastro-enterology and Tuberculosis will be held at the same times and places.

(2) American Board of Pediatrics; John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. Oral Examinations—Richmond, Va., February 10, 11, 12, 1950; Philadelphia, Pa., March 31, April 1, 2, 1950; San Francisco, Calif., June 23, 24, 25, 1950.

Courses in Laboratory Training Offered by the Communicable Disease Center, Atlanta

The Communicable Disease Center of the Federal Security Agency of the Public Health Service, 291 Peachtree St., Atlanta, Ga., announces the following laboratory training courses during 1950:

Rickettsial Serology, January 9–13, Chamblee, Ga.
Arthropod Identification, February 13–24, Atlanta, Ga.
Parasitology, Part I, March 27–April 14, Atlanta, Ga.
Parasitology, Part II, April 17–May 5, Atlanta, Ga.
Rabies, May 8–12, Atlanta, Ga.
Bacterial Diseases (Directors), May 22–26, Chamblee, Ga.
Mycotic Diseases (Directors), May 29–June 2, Chamblee, Ga.
Tuberculosis (Directors), June 5–9, Chamblee, Ga.
Parasitology (Directors), June 12–16, Atlanta, Ga.
Mycotic Diseases, Part I, Cutaneous and Subcutaneous Fungi, July 24–August 4, Chamblee, Ga.
Mycotic Diseases, Part II, Systemic Fungi, August 7–17, Chamblee, Ga.
Tuberculosis, August 21–September 7, Chamblee, Ga.
Bacterial Diseases, Part I, September 11–22, Chamblee, Ga.
Bacterial Diseases, Part II, September 25–October 6, Chamblee, Ga.
Parasitology, Part I, September 18–October 6, Atlanta, Ga.
Parasitology, Part II, October 9–27, Atlanta, Ga.
Enteric Diseases, Part I, October 9–13, Chamblee, Ga.
Enteric Diseases, Part II, October 16–27, Chamblee, Ga.
Identification of Medically Important Arthropods, November 13–24, Atlanta, Ga.
Virus Isolation and Identification Technics, November 13–17, Montgomery, Ala.
Laboratory Diagnosis of Influenza, November 20–24, Montgomery, Ala.
Laboratory Diagnosis of Rabies, November 27–December 1, Montgomery, Ala.

The Communicable Disease Center, by special arrangement, also offers courses in Laboratory Diagnosis of Malaria, of Virus Diseases, and Phage Typing of *Salmonella typhosa*.

Fellowships in Allergy

Applications are being accepted by the Division of Allergy, Northwestern University Medical School, Chicago, for two Fellowships in Allergy, one being available on July 1, 1950, the other on January 1, 1951. These Fellowships are for the specific purpose of affording clinical training in allergy and related fields while allowing time for laboratory research. Prerequisite experience is two years postgraduate training approved by the American Board of Internal Medicine or the American Board of Pediatrics. The fellowship training program is approved by the Council on Medical Education and Hospitals of the American Medical Association and is accredited by the above specialty boards. The stipend ranges from $2,400 to $3,500.

International Pharmacopoeia Proposed

The World Health Organization, according to a recent statement, is urging the preparation of an International Pharmacopoeia. Differences in national standards for widely used materials constitute a source of danger to travelers who may need to have the same prescription dispensed in different countries. Uniformity in drugs is also of great importance in trade between countries and in medical research, since the conclusions of doctors working to discover the best drug or the best forms of giving drugs may become valueless, if it is not known exactly to what strength of drug or type of drug those conclusions refer. The different national pharmacopoeias may also give different names to the same drug.

Grants for Non-Federal Heart Research Projects

Award of $60,961 in Public Health Service grants for four non-federal heart research projects investigating hardening of the arteries, high blood pressure, and the effect of chemical and electrical substances on the heart, has been announced by Acting Federal Security Administrator, John L. Thurston. The grants were made by the National Heart Institute to three medical schools and a private foundation, including Duke University School of Medicine, Harvard Medical School, the Cleveland Clinic Foundation, and the University of Louisville.

Duke University School of Medicine will investigate the mechanism by which the rice diet benefits patients with high blood pressure. Harvard Medical School will investigate various chemical compounds for properties which will counteract heart-stimulating substances released by the body. The Cleveland Clinic Foundation will investigate the endocrine glands to determine their rôle in the development of high blood pressure and hardening of the arteries. The University of Louisville will investigate muscle activity. These grants are in addition to other grants announced last month. With these new awards heart grants approved since July 1, 1949, have reached a total of 368, amounting to $10,251,778 in Public Health Service Funds granted to non-federal institutions for heart research.

Army Internship Appointments

Major General R. W. Bliss, F.A.C.P., Army Surgeon General, has announced 190 senior medical students have been appointed to Army internships beginning next July 1. These represent the Army's selections out of 1,014 candidates who applied for both Army and Air Force internships.

Sixty-four of the 71 approved medical schools in the country are represented in the group of selectees, 96 per cent of whom are former service men. Sixty-one are former non-commissioned technicians and specialists. One hundred and one are former Army commissioned personnel. Upon graduation from medical school each will be commissioned a first lieutenant in the Army Medical Corps Reserve, called to extended active duty, and assigned for internship to one of the 10 Army General Hospitals, which are approved for intern training.

New Building Plans, Army Medical Library

The General Services Administrator has given assurance that funds would be budgeted for the construction of a new building for the Army Medical Library, authorizing legislation to be presented at the next session of Congress. The question of location is urgent. The Association of Honorary Consultants at their annual

meeting agreed that the question of location should not be allowed to impede the Library's progress toward its new building.

The Office of the Librarian of the Army Medical Library has been abolished and a new position "Assistant to the Director" has been created. Mr. Scott Adams has been selected to fill this position.

Fellowships Offered by National Foundation for Infantile Paralysis

The National Foundation for Infantile Paralysis has announced postgraduate research fellowships for one to three years in the fields of virology, orthopedic surgery, pediatrics, epidemiology and neurology. These fellowships are available to properly qualified candidates whose objectives are research and teaching in these fields. Eligibility requirements include United States citizenship; sound health; degree of Doctor of Medicine or Doctor of Philosophy; two years' residency training in the specialty; and a program of study and detailed plan of investigation. Financial benefits will be arranged according to individual needs. Candidates will be selected competitively by a committee of scientists and clinicians. Information and applications are obtainable from Professional Education Division, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

American Society for the Study of Sterility

The American Society for the Study of Sterility will meet at the Sir Francis Drake Hotel, San Francisco, Calif., June 24–25, 1950.

The Society is offering an annual award of $1,000, known as the Ortho Award, for an essay on the result of some clinical or laboratory research pertinent to the field of sterility. Competition is open to those who are in clinical practice as well as to individuals whose work is restricted to research in basic fields or full-time teaching positions. The Prize Essay will appear on the program of the forthcoming meeting. For further particulars, consult Dr. Walter W. Williams, Secretary, 20 Magnolia Terrace, Springfield, Mass.

University of California Postgraduate Program

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction at the University of California Medical Center, San Francisco 22, Calif., announces numerous postgraduate courses of interest to the practicing physician, among these being:

Applied Therapeutics, January 30–February 1.
Electrocardiography, January 30–February 1.
Special Problems in Pediatrics, February 6–10.
Forensic Medicine, February 6–8.
Gastro-enterology, August 28–30.
Psychiatry and Neurology, August 28–November 17.
There are also several courses in the surgical field.

Annual Rudolph Matas Lecture

The third annual Rudolph Matas Lecture, held each year in honor of Dr. Rudolph Matas, Emeritus Professor of Surgery at the Tulane University of Louisiana School of Medicine, was presented by Dr. Cecil J. Watson, F.A.C.P., Professor of Medicine at the University of Minnesota, at the Hutchinson Memorial, Tulane University,

January 27, 1950. Dr. Watson's title was "Modern Concepts of Liver Function and Their Alteration in Disease." The lecture was given under the auspices of Nu Sigma Nu Medical Fraternity.

Established in 1947 by the Tulane Chapter of Nu Sigma Nu to honor Dr. Matas, who served for 27 years as Professor of Surgery at Tulane, the lectureship is designed to bring outstanding specialists in the various fields of medicine and surgery to New Orleans. Dr. Alfred Blalock of Johns Hopkins University presented the initial lecture and Dr. William C. Menninger, F.A.C.P., of the Menninger Clinic, Topeka, Kansas, gave the following lecture.

Texas Academy of Internal Medicine Recently Formed

The Texas Academy of Internal Medicine was recently formed and Dr. Samuel A. Shelburne, F.A.C.P., Dallas, was elected its first President, and Dr. Edward A. Wilkerson, F.A.C.P., Houston, Vice-President. According to the early announcements, physicians to be eligible for membership in the new Society must be diplomates of the American Board of Internal Medicine and Fellows of the American College of Physicians.

Thomas Parran Scholarship

Former associates in the U. S. Public Health Service of Dr. Thomas Parran, F.A.C.P., recently established a Thomas Parran Scholarship at the Pittsburgh Graduate School of Public Health, connected with the University of Pittsburgh. The principal of the fund, $5,000, will be administered by the University. Additional contributions may later be added. Income from the Fund will be used for tuition fees for one student each session. Dr. Parran was the former Surgeon General of the U. S. Public Health Service and since 1948 has been Dean of the Graduate School of Public Health of the University of Pittsburgh. The school is not yet in operation, so far as enrollment of students is concerned, but many appointments are being made to the faculty in preparation for the formal opening.

Dr. Thomas M. Durant, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia; Dr. John B. Levan, F.A.C.P.,Chief, Cardiac Clinic, St. Joseph's Hospital, Reading; Dr. Charles W. Smith, F.A.C.P., Dr. Constantine P. Faller, F.A.C.P., and Dr. Kenneth E. Quickel, F.A.C.P., all of Harrisburg, constitute the faculty of a course in Electrocardiography sponsored by the Medical Society of the State of Pennsylvania and conducted on seven consecutive Thursdays, starting last November 10, at the Harrisburg Hospital. It was announced that 60 physicians, coming from 40 different Pennsylvania counties, were enrolled.

National Gastro-Enterological Association Announces 1950 Prize Award

The National Gastro-Enterological Association offers a $100.00 cash award and a Certificate of Merit for the best unpublished contribution on gastro-enterological or allied subjects. Contestants must be members of the chief national medical association of their countries. Entries for the 1950 prize should be limited to five thousand words, be typewritten in English, prepared in manuscript form, submitted in five copies, accompanied by an entry letter, and must be received not later than June 1, 1950, at the headquarters of the National Gastro-enterological Association, 1819 Broadway, New York 23, N. Y. Certificates will be awarded at the Annual Convention Banquet of the Society.

Dr. Herbert S. Gaskill (Associate) has been appointed Professor of Psychiatry at Indiana University School of Medicine in connection with the further expansion of the full time staff of that institution. Dr. Gaskill will integrate psychiatric teaching and consultation into the teaching of medicine, surgery, pediatrics and obstetrics.

The Annual Meeting of the Association for Research in Nervous and Mental Diseases was held at New York, December 2–3, 1949, under the presidency of Dr. Harold G. Wolff, F.A.C.P. The meeting was devoted to "Life Stress and Bodily Disease."

American Institute of Nutrition Announces Awards

The American Institute of Nutrition invites nominations for three awards to be made at its annual meeting during the Spring of 1950: (1) The Osborne and Mendel Award of $1,000 for recognition of outstanding accomplishments in the general field of exploratory research in the science of nutrition; the award to be made for the most significant published contribution in 1949 or for a series of contemporary papers of outstanding significance. (2) The Mead Johnson & Company Award of $1,000, to promote researches dealing with the B complex vitamins. This award will be given to the laboratory or clinical research worker in the United States or Canada who has published the most meritorious work dealing with the field of B complex vitamins during 1949. The judges, however, are given considerable latitude in the exercise of their function. (3) The Borden Company Foundation Award of $1,000 and a gold medal, in recognition of distinctive research by investigators in the United States and Canada which emphasizes the nutritive significance of the components of milk or of dairy products. This award will be made primarily for the publication of specific papers either during 1949 or over an extended period of time.

Nominations should be accompanied with full data concerning the nominee and his research to: Osborne and Mendel Award, Dr. H. E. Carter, University of Illinois, Urbana; Mead Johnson and Company Award, Dr. W. H. Sebrell, Jr., National Institute of Health, Bethesda, Md.; Borden Award, Dr. L. A. Maynard, Cornell University, Ithaca, N. Y.

Postgraduate Course in Endocrinology and Diabetes

Dr. Henry H. Turner, F.A.C.P., Secretary-Treasurer, Association for the Study of Internal Secretions, 1200 North Walker St., Oklahoma City, is supervising a postgraduate course in Endocrinology and Diabetes to be held at the Roney-Plaza Hotel, Miami Beach, Florida, April 3–8, 1950. The program is directed not only to the specialist but to the general practitioner, and will consist of lectures, clinics and demonstrations. The faculty will include prominent investigators and clinicians in the field of endocrinology and metabolic disorders. The matriculation fee is $75.00.

Dr. Snell Elected Member, American Board of Internal Medicine

Dr. Albert M. Snell, F.A.C.P., has been appointed a member of the American Board of Internal Medicine to fill the unexpired term of Dr. Cecil J. Watson, F.A.C.P., resigned, to July 1, 1950.

Dr. Youmans Becomes Dean at Vanderbilt University

Dr. John B. Youmans, F.A.C.P., who has been Dean of the University of Illinois College of Medicine, Chicago, since 1946, has resigned to accept deanship of Vander-

bilt University School of Medicine, Nashville, Tennessee, as of March 1, 1950. Dr. Youmans was associated with Vanderbilt University from 1927 to 1946, and from 1930 to 1946 was Director of Postgraduate Instruction there.

Dr. Tinsley R. Harrison, F.A.C.P., Professor of Medicine, Southwestern Medical College, Dallas, Texas, delivered the annual Clarence M. Jackson Lecture at the University of Minnesota Medical School, Minneapolis, on January 6, 1950, his title being "The Evaluation of Cardiac Murmurs."

Colonel Wesley C. Cox (MC), U. S. Army, F.A.C.P., Commanding Officer, Industrial Hygiene Laboratory, Army Chemical Center, Maryland, represented the U. S. Army and the American Association of Industrial Physicians and Surgeons at the First Inter-American Conference on Industrial Medicine at Buenos Aires, December 1–15, 1949.

Major General Harry G. Armstrong Becomes Surgeon General, U. S. Air Force

Major General Harry G. Armstrong, F.A.C.P., on December 1, became the new Surgeon General of the U. S. Army Air Force, succeeding Major General Malcolm C. Grow, retired. Brigadier General Dan Clark Ogle (Associate) became the Deputy Surgeon General.

Dr. Joseph F. Sadusk, Jr., F.A.C.P., has retired as Executive Director of the Committee on Medical Sciences of the Research and Development Board, Department of Defense, and has joined the faculty of Stanford University School of Medicine. During the war, Dr. Sadusk was executive officer of the U. S. Typhus Commission and was awarded the Typhus Commission Medal. Later he was Associate Medical Director of the Prudential Insurance Company of America and in 1946 returned to Yale University School of Medicine as Assistant Professor of Medicine.

Dr. Seale Harris Honored

Dr. Seale Harris, F.A.C.P., Birmingham, Ala., was the recipient of the Research Medal of the Southern Medical Association at its annual meeting in Cincinnati. The award was made in recognition of Dr. Harris' original research in hyperinsulinism and for his work in the fields of nutrition, metabolism and diabetes mellitus. The American Medical Association in June, 1949, awarded Dr. Harris the Distinguished Service Medal for his work on hyperinsulinism.

Dr. J. Arthur Myers Honored

Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn., was given a plaque for distinguished service in tuberculosis control at the annual Christmas Seal dinner of the Minnesota Public Health Association, October 25, 1949.

Dr. Myers is Professor of Internal Medicine, Preventive Medicine and Public Health at the University of Minnesota and is a past president of the National Tuberculosis Association, Mississippi Valley Conference on Tuberculosis, American College of Chest Physicians and the Minnesota Public Health Association. He is a member of the editorial board of the "American Review of Tuberculosis" and Editor-in-Chief of the official publication of the American College of Chest Physicians, "Diseases of the Chest."

Dr. Kenneth M. Lynch, F.A.C.P., Dean of the Medical College of the State of South Carolina, Charleston, has been elected President of that institution.

School of Hospital Administration

The Medical College of Virginia, Richmond, has established a School of Hospital Administration to prepare men and women for careers in the field of hospital administration. The new school opened on January 2, 1950.

Dr. Malcolm T. MacEachern Appointed Director of American College of Surgeons

Dr. Malcolm T. MacEachern, F.A.C.P., Associate Director of the American College of Surgeons since 1923, was recently appointed Director of the College. He has been Chairman of the Administrative Board of the College since 1935, and is Professor of Hospital Administration at Northwestern University. He is probably best known as the Director of the Hospital Administration Program of the College, work that he has directed for many years. He is a graduate of McGill University Faculty of Medicine.

Dr. Jacob M. Cahan, F.A.C.P., Philadelphia, has donated to the College Library a copy of "The Heart and the School Child," edited by him. Many Fellows of the College are among the contributors.

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, has been elected President of the Pittsburgh Allergy Society for the period 1949–1951.

At a presentation ceremony held by the Lieutenant-Governor of Nova Scotia at Government House, Halifax, November 12, 1949, Dr. E. David Sherman, F.A.C.P., New York, N. Y., was awarded Honorary Life Membership in the St. John Ambulance Association of The Venerable Order of the Hospital of St. John of Jerusalem.

Dr. Louis F. Bishop, Jr., F.A.C.P., New York, N. Y., addressed the 1949 Annual Meeting of the Southern Medical Association at Cincinnati on "Psychosomatic Aspects of Cardiovascular Disease."

CORRECTION

On page 938 of the November, 1949, issue of this Journal, in the report of the gift of an old manuscript by Dr. S. T. Laufer, F.A.C.P., to the College, the date of the manuscript was erroneously recorded as "1709" whereas it should have been "1309." It was a manuscript on Clinical Medicine by Nicholaus Corazzelli done in longhand and in Latin.

OBITUARIES

DR. SPENCER AUGUSTUS FOLSOM

The sudden death of Dr. Spencer Folsom, F.A.C.P., at his home in Orlando, Florida, on June 26, 1949, brought a great sense of loss to his many friends, patients and colleagues.

Dr. Folsom was born August 15, 1895, in San Francisco, California. He received his M.D. degree from the Emory University School of Medicine in 1917. He served as a medical officer with the Marine Corps in World War I. He was chief resident at Grady Memorial Hospital, Atlanta, Georgia, 1923–1924, and was visiting physician, 1924–1925. He began the practice of medicine in Orlando, Florida, in 1926. He was chief of the medical service, Orange Memorial Hospital, consultant in medicine, Florida Sanitarium and Hospital at the time of his death.

A Fellow of the American College of Physicians since 1930, and a Life Fellow since 1943, Dr. Folsom was also a member of the Orange County Medical Society, Florida State Medical Association, Southern Medical Association, and Fellow, American Medical Association.

He was attentive to details, kind and thorough, never sparing himself in his duty to his patients. He was beloved by those he served, and is mourned by a host of friends, professional and lay, who will always remember and miss his genial personality.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. FLOYD HEATON LASHMET

Dr. Floyd Heaton Lashmet, of Petoskey, Michigan, was born in Manchester, Illinois, on September 12, 1898. He received his B.S. degree in 1920 from the University of Illinois; Master of Science in 1925, University of Michigan, and M.D. in 1927 from the University of Michigan Medical School. Following graduation, he was for several years associated with Dr. Newburgh at the University of Michigan Medical School as Research Assistant Instructor and finally Assistant Professor of Medicine. During this period, he contributed considerably to the literature, especially regarding metabolic diseases and, in particular, diabetes mellitus. In 1934, he left the University and went into private practice in Petoskey, Michigan. He served as Chief of the Medical Service at the Lockwood General Hospital and continued his affiliation until his death on October 24, 1949.

Dr. Lashmet was a member of his county and state medical societies and the American Medical Association. He also was a member of the Central Society for Clinical Research and the American Society for Clinical Investigation. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1934.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. FREDERICK CLYDE POTTER

It is with deepest regret that the professional colleagues both within and without the American College of Physicians have learned of the passing of Frederick Clyde Potter, M.D., F.A.C.P., on September 24, 1949, at Cuyahoga Falls, Ohio.

Born in Jenningsville, Pa., on July 10, 1882, Dr. Potter was graduated from the Medico-Chirurgical College of Philadelphia in 1909. Early in his career he served as Assistant in the Norristown (Pa.) State Hospital, and later as Pathologist at the Central Hospital in Indianapolis. At this same time he was Assistant Professor of

Nervous and Mental Diseases in the Indiana University School of Medicine. Later he served as Pathologist at the Kalamazoo (Mich.) State Hospital, and again later was Assistant Medical Director at Mercer Sanitarium at Mercer, Pa.

During World War I, he served as Neuropathologist to the United States General Hospitals No. 11 and No. 41, respectively. He then went to Akron, Ohio, as Pathologist at the Peoples, Children's and St. Thomas Hospitals. He also served St. Thomas and Citizens Hospitals at Barberton, Ohio, as Pathologist.

During World War II, Dr. Potter became Chief of Laboratory Service, Billings General Hospital, Ft. Benjamin Harrison, Indiana, serving with the rank of Major, Medical Reserve Corps, U. S. Army. He continued in this relationship until retirement from active duty because of physical disability, April, 1945, with the rank of Lieutenant Colonel.

Dr. Potter was President of the Summit County (Ohio) Medical Society in 1929. He was a Diplomate of the American Board of Pathology, and he made basic contributions to this, his chosen professional field, as he served his country in two World Wars, and the various communities in Pennsylvania, Indiana, Michigan and Ohio, where he lived. Those who knew Dr. Potter sensed his sincere interest in the problems of the mechanism of disease as reflected in the pathologic processes he saw both clinically and at the autopsy table, and found him always a stimulating consultant.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. E. MARSH WILLIAMS

Dr. E. Marsh Williams, a Fellow of the American College of Physicians, died at Oskaloosa, Iowa, May 17, 1949, after a prolonged illness. He was born in 1870 and held degrees of A.B. from the University of Kansas, B.S. from the University of Chicago, and M.D. from Rush Medical College, 1905. He served at various times as Professor of Biology at Friends University in Wichita, Kans., as Professor of Pathology and Bacteriology at the State University of Oklahoma, and as Instructor in Pharmacology and Materia Medica at St. Louis University School of Medicine.

For many years he was the Health Officer of the City of Oskaloosa, Iowa. Dr. Williams was a former President of the Iowa State Public Health Association, of the Mahaska (Iowa) County Medical Society, and of the Oskaloosa Kiwanis Club. He was a member of the Iowa State Board of Health and a member of the Board of Directors of the Iowa Tuberculosis Association. He became a Fellow of the American College of Physicians in 1920.

E. R. L.

DR. M. LAWRENCE TURNER

Dr. M. Lawrence Turner, Fellow of the American College of Physicians since 1926, died in St. Petersburg, Florida, on June 6, 1949.

Dr. Turner was born in New York City on May 28, 1870, received his M.D. degree from Long Island College Hospital in 1893 and interned at the Children's Hospital, Randall's Island, N. Y., and at the Emergency Hospital, Washington, D. C. He served as Surgeon with the Panama Canal Company before the United States became involved in that enterprise. From 1898 to 1900, he served as Acting Assistant Surgeon in Cuba with the U. S. Army during the Spanish-American War. Later on he entered the Army officially and held the commission of Lieutenant Colonel. From 1910 to 1915, he was in private practice in Washington, D. C., and in some subsequent years conducted a limited practice at Berwyn, Md. He maintained a winter home in St. Petersburg, Fla., for many years and about 1935 removed to that city as his permanent, year-round address.

Dr. Turner was an enthusiastic Fellow of the American College of Physicians and was the fourth in the history of the College to become a Life Member. He gave many books to the College Library, one being a very unusual medical book published in Latin and printed from wood cuts at Leipzig, Germany, in the middle of the 17th Century. At different times, he made contributions of funds to such organizations as the Truesdale Hospital of Fall River, Mass., the Sibley-Memorial Hospital of Washington D. C., and the University of Maryland. He had been a member of the District of Columbia Medical Society, the National Tuberculosis Association, the American Association for the Advancement of Science, the Association of Military Surgeons of the United States, and a Fellow of the American Medical Association.

His life was marked by generosity and an abiding interest in promoting the welfare of the medical profession and advancing medical science.

E. R. L.

DR. ERNEST KELLEY

Ernest Kelley, M.D., F.A.C.P., born Des Moines, Iowa, December 20, 1883; died May 14, 1949. M.D., 1907, Creighton University School of Medicine.

Dr. Kelley served on the faculty of Creighton University School of Medicine for many years, advancing from Assistant Professor of Neuropsychiatry to a full professorship and Director of the Department in 1939. He was neuropsychiatrist on the following hospital staffs: Creighton Memorial, St. Joseph's, Doctors, St. Catherine's Lutheran, Douglas County, Omaha; and St. Bernard's, Council Bluffs, Iowa.

He was a Diplomate of the American Board of Psychiatry and Neurology; Fellow of the American Medical Association, Fellow of the American College of Physicians since 1929; Member, American Psychiatric Association, Nebraska State Medical Association, Omaha-Douglas County Medical Society, and the Omaha Mid-West Clinical Society.

Dr. Kelley was a highly capable teacher and clinician and had many intellectual interests. He was greatly admired by the numerous students who came under his supervision. Dr. Kelley ennobled his profession and his influence will long be cherished as an example and inspiration.

J. D. McCarthy, M.D., F.A.C.P.,
Governor for Nebraska

ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 13, 1949

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., November 13, 1949, with President Reginald Fitz presiding, Mr. E. R. Loveland, Secretary, and the following in attendance: Reginald Fitz, *President;* William S. Middleton, *President-Elect;* Turner Z. Cason, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, Wallace M. Yater, Edward L. Bortz, Harold H. Jones, William S. McCann, T. Grier Miller, Charles F. Moffatt, Walter L. Palmer, *Chairman, Board of Governors;* Maurice C. Pincoffs, *Editor,* ANNALS OF INTERNAL MEDICINE; Thomas M. McMillan, *Chairman, Advisory Committee on Postgraduate Courses;* and Truman G. Schnabel, *Chairman, American Board of Internal Medicine.*

The Secretary read abstracted Minutes of the preceding meetings of the Board of Regents, which, upon motion seconded and carried, were approved.

The Secretary then presented the following communications:

(1) From absent Regents—Doctors R. R. Snowden, David P. Barr and George F. Strong—who, because of extenuating circumstances, could not be present.

(2) Letter from the American Board of Internal Medicine, stating that Dr. Albert M. Snell, Rochester, Minn., had been selected from the three nominees by the Board of Regents, at its preceding meeting, as the successor to Dr. Cecil J. Watson, resigned, for term expiring June 30, 1950.

(3) Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C., was appointed by the President and served as the official representative of the College at the installation ceremonies of the new President, Arthur Hollis Edens, of Duke University, Durham, N. C., on October 22, 1949.

(4) A communication from Dr. Harold R. Carter, F.A.C.P., Denver, Colo., signed by eleven additional Fellows, emphasizing their desire that the selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective territories.

(5) An announcement that Dr. Charles H. Drenckhahn, F.A.C.P., Urbana, Ill., had been appointed by President Fitz as interim Governor for Southern Illinois, until the next regular election, to fill the vacancy caused by the death of Dr. Cecil M. Jack, former Governor.

(6) A report that in accordance with authority vested in the President, Dr. Fitz had made the following appointments as representatives and alternates to the United States Pharmacopoeial Convention, Washington, D. C., May 9–10, 1950:

	Alternates
Walter W. Palmer, *Chairman*	David P. Barr
Chester S. Keefer	William S. McCann
Marion A. Blankenhorn	Walter B. Martin

(7) Presentation of a suggested draft for the Honorary Fellowship Certificate prepared by the Secretary and Secretary-General, in accordance with directions of the Board of Regents. The draft was by resolution unanimously approved.

(8) A report from the Secretary that Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, who directed one of the A.C.P. postgraduate courses, had donated $375.00 of the proceeds for the purchase of projection equipment for the College Auditorium. A 16 mm. Envoy Victor Sound Projector and a Bessler Slide Stereopticon were purchased, in accordance with Dr. Leaman's wish, and were on display.

On motion by Dr. A. B. Brower, seconded by Dr. Wallace M. Yater, and unanimously carried, a resolution was adopted expressing the appreciation of the Board of Regents to Dr. Leaman.

(9) A report from the Secretary that under the will of the late Dr. William Gerry Morgan, M.A.C.P., one of the original Founders of the College, the College Historian and a former Secretary-General, the College is to receive Dr. Morgan's diplomas and a collection of important autographed photographs, including some of past Presidents of the United States, distinguished physicians, and others.

On motion by Dr. Cyrus C. Sturgis, seconded by Dr. Maurice C. Pincoffs, and unanimously carried, the President was instructed to send a letter of appreciation to Mrs. William Gerry Morgan.

(10) A series of letters, initiated by Dr. S. Marx White, F.A.C.P., of Minneapolis, embodying a combined invitation from practically all medical agencies in Minnesota for the College to hold its 1953 Annual Session in Minneapolis.

President Fitz asked for a discussion of the communication from Dr. Harold R. Carter, about the election of the Governor for Colorado, asking for opinions as to whether or not Governors should be elected through some caucus method, introducing the possibility of medical politics in the selection of Governors.

It was moved by Dr. Walter L. Palmer, seconded and carried, that the Secretary advise Dr. Harold R. Carter, stating his communication had been received and discussed by the Board of Regents, that assurance be given that each Committee on Nominations is always given the directions embodied in the By-Laws, and requested to attempt to follow them.

Dr. George Morris Piersol, Secretary-General, presented the following report:

(1) Deaths since last meeting of this Board (2 Masters; 38 Fellows; 9 Associates):

Masters

Miller, Sydney R.	Baltimore, Md.	May 25, 1949
Morgan, William Gerry	Washington, D. C.	July 7, 1949

Fellows

Addis, Thomas	Los Angeles, Calif.	June 4, 1949
Alling, Frederic A.	Newark, N. J.	October 20, 1949
Anderson, Edward Waldemar	Des Moines, Iowa	September 5, 1949
Anderson, Wilhelm S.	Northfield, Minn.	June 26, 1949
Barker, W. Halsey	Baltimore, Md.	March 26, 1949
Blue, William Ramsey	Memphis, Tenn.	September 8, 1949
Cade, William Henry	San Antonio, Tex.	July 4, 1949
Chambers, Wilfred Ernest	Indianapolis, Ind.	September 26, 1949
Cook, George Lindsay	Tampa, Fla.	March 8, 1949
Cullen, Victor Francis	Baltimore, Md.	March 9, 1949

Douglas, Bruce Hutchinson	Detroit, Mich.	August 11, 1949
George, Shaul	Pittsburgh, Pa.	April 14, 1949
Graves, William Washington	St. Louis, Mo.	April 19, 1949
Greenbaum, Sigmund Samuel	Philadelphia, Pa.	October 3, 1949
Jack, Cecil McKee	Decatur, Ill.	June 28, 1949
Kelley, Ernest	Omaha, Nebr.	May 14, 1949
Lewis, Thomas Krapfel	Camden, N. J.	August 28, 1949
Litvak, Abraham M.	Brooklyn, N. Y.	January 28, 1949
Lockard, G. Carroll	Baltimore, Md.	August 7, 1949
Louria, Alexander Leon	Brooklyn, N. Y.	May 22, 1949
Meehan, John William	M.C., U. S. Army	May 28, 1949
Muniz, Jorge R.	Havana, Cuba	May 21, 1949
Pemberton, Ralph	Philadelphia, Pa.	June 17, 1949
Plummer, William Albert, Sr.	Rochester, Minn.	March 22, 1949
Potter, Frederick Clyde	Cuyahoga Falls, Ohio	September 24, 1949
Redwood, Frank Harrell	Norfolk, Va.	May 27, 1949
Reid, William Duncan	Kezar Falls, Maine	September 29, 1949
Rudisill, Hillyer, Jr.	Charleston, S. C.	July 27, 1949
Rutledge, Clifford P.	Shreveport, La.	January 31, 1949
Simonds, Paul Edward	Riverside, Calif.	July 10, 1949
Skinner, George A.	M.C., U. S. Army	May 15, 1949
Soley, Mayo Hamilton	Iowa City, Iowa	June 21, 1949
Thomas, Anne Heath	Colorado Springs, Colo.	May 21, 1949
Torbett, John Walter, Sr.	Marlin, Tex.	August 9, 1949
Turner, Molyneaux Lawrence	St. Petersburg, Fla.	June 6, 1949
West, Randolph	New York, N. Y.	May 20, 1949
Willhelmy, Ellis W.	Kansas City, Mo.	May 5, 1949
Williams, E. Marsh	Oskaloosa, Iowa	May 17, 1949

Associates

Ben-Asher, Solomon	Jersey City, N. J.	April 27, 1949
Elgart, Samuel	Cincinnati, Ohio	June 18, 1949
Gichner, Joseph E.	Baltimore, Md.	March 8, 1949
Hall, Frederic Wilhelm	Ponca City, Okla.	May 21, 1949
Hargis, William H., Jr.	San Antonio, Tex.	August 15, 1949
Martin, Albert Rankin	Chicago, Ill.	October 13, 1948
Ward, Frederick Erastus	Easton, Pa.	May 4, 1949
Westmoreland, Robert E., Sr.	Indianapolis, Ind.	June 30, 1949
Westra, Jacob John	Champaign, Ill.	July 17, 1949

The Regents stood in silence in memory of the departed members. President Fitz noted particularly the deaths of Dr. Sydney R. Miller, a past President of the College; Dr. William Gerry Morgan, a past Secretary-General, the Historian and a Founding Fellow of the College; and Dr. Cecil M. Jack, a Governor of the College; each one of whom has played an important part in the administration of the College, and that it would seem fitting to have a special Minute appear with regard to these three men, in order that it may appear in the official records of the Board of Regents, and that this be prepared by the Secretary-General.

A resolution was adopted approving the recommendation of the President.

The Secretary-General continued his report:

(2) Additional Life Members since last meeting of this Board (14)—this makes a grand total of 799, of whom 69 are deceased, leaving a balance of 730.

Arthur W. Phillips	Philadelphia, Pa.
Clarence H. Webb	Shreveport, La.
Walter L. Bierring	Des Moines, Iowa
Robert Martin Moore	Indianapolis, Ind.
William V. Conn	Greensburg, Pa.
Clark P. Pritchett	Columbus, Ohio
Samuel J. Schneierson	New York, N. Y.
William E. G. Bayley	La Fayette, Ind.
Joseph Edward Walther	Indianapolis, Ind.
Joseph Augustine Lundy	Worcester, Mass.
Terence Lloyd Tyson	New York, N. Y.
Ernest W. Willetts	Pittsburgh, Pa.
Wallace Lamar Poole	Johnson City, Tenn.
Reginald Fitz	Boston, Mass.

The Secretary then presented the following report: "Before I start my report, I want to announce that Dr. A. B. Brower has delivered into our hands at this meeting an additional check for $2,500.00, a part of his original gift to the College for the establishment of a traveling fellowship, this bringing Dr. Brower's gift up to a total of $7,500.00." (Applause.)

MR. E. R. LOVELAND: "Mr. Frederick Pindar, our erstwhile assistant, resigned August 31, 1949, to accept an appointment with Stanford University's Laboratories at Palo Alto, Calif. One of his important assignments in the College was the editing of the new and revised Directory of the College, which we had expected to be completed by the time of his release. Mr. Pindar had accomplished no more than one-quarter of the work when he relinquished his services. Mr. David Horn was brought in as his successor, has been diligently at work exclusively on the Directory since that time, and it is confidently expected that the work will be completed during December and the Directory distributed.

"Mr. Horn has been appointed as Executive Assistant. He is a graduate of the Wharton School of the University of Pennsylvania, and has had fourteen years valuable experience, and it is expected that he will develop into a valuable and capable assistant.

"We desire to recommend to the Board of Regents that Miss Pearl M. Ott who is certainly one of the most valuable and loyal members of our staff, and by far the most experienced, be designated, like Mr. Horn, as 'Executive Assistant.'

"We are gratified to report to the Regents that we have operated in all departments within the budget appropriations for 1949, and expect to conclude 1949 with a balance of approximately $7,000.00 within the amount appropriated.

"We are also gratified to report that the publication of the ANNALS has continued in a most satisfactory manner. The circulation has increased within the past year approximately 1,400. One year ago (October) we were printing 12,200 copies; now, 13,600 copies.

"We should be well pleased with the progress of our Regional Meetings. The number has continued to grow somewhat, the attendance and member participation have increased. We have prepared for you a duplicated outline of the Regional Meetings conducted during 1949, and we wish to express our appreciation for the aid given by the President, the President-Elect and the other Officers and Regents who have attended these meetings on behalf of the Central Office of the College. As an illustration of the service performed for the College, I wish to read one Governor's letter, that of Puerto Rico, concerning the College Regent who represented the College at his recent Regional Meeting (reads letter from Governor Rodriguez-Molina, of Puerto Rico).

"'The Postgraduate Course Program continues to be one of our most popular activities. A more detailed report will be received from the Chairman of the Advisory Committee on Postgraduate Courses. One of my secretaries devotes her full time to this work. We believe the College program has been a model for all concentrated, intensive courses of an advanced nature. Our program is adequate for the needs of our members; the registration is highly satisfactory.

"'We are all hard at work on the preparations for the Thirty-first Annual Session in Boston, April 17–21, 1950. We shall have one of the best planned Exhibits in our history, and we predict a larger net income therefrom than ever before. Information concerning the program and arrangements will be reported later by the proper officials. The Officers, Regents and Governors will be housed at Hotel Statler, and we shall provide accommodations and directions later. In accordance with directions of this Board, the attendance will be restricted to members of the College and guests who are directly sponsored by members. The non-member fee is to be increased from $15.00 to $25.00. In these two manners we expect to accommodate our members in a thoroughly satisfactory manner.'"

(By resolution the report of the Executive Secretary was accepted and approved.)

The President called upon the Chairman of the Committee on Credentials, Dr. Piersol, to present his report.

Dr. George Morris Piersol: "All members of the Committee on Credentials were in session Friday and Saturday, November 11–12, 1949, and presents the following report:

"(1) The Board of Regents on March 29, 1949, referred to the Committee on Credentials the problem of solving membership requirements for candidates outside of the United States and Canada in regard to the matter of certification. In view of the fact that citizens of other countries of North America, other than the United States or Canada, are not eligible for admission to the examinations of the American Board of Internal Medicine, and in view of the fact that there are no comparable boards of certification in those countries, the Committee on Credentials is of the opinion that the College shall in effect eliminate Associateship from those countries and only admit the most distinguished physicians and then to Direct Fellowship. The Committee, furthermore, is favorable to the establishment of a Governorship in each of those countries if, as and when they qualify for such representation."

(On motion by Dr. Piersol, seconded and duly carried, this portion of the report was approved.)

Dr. Piersol then presented items (2), (3) and (4) from his report, which included the official removal from the Associate Roster of a candidate who desired not to accept election in that category; the acceptance of the resignation of an Associate whose term would expire at this meeting, due to his having been unable to qualify for Fellowship, including certification by the American Board, and who requested permission to apply for reinstatement at some future time, when he shall have completed the customary qualifications; the application of an Associate for an extension of his Associate term who had been unable to attain certification, thus to qualify for Fellowship in the maximal term allowed.

By resolution the Board approved the recommendation of the Committee to remove the name of the Associate from the Roster, in the category of a resignation, and of the acceptance of the formal resignation of the second Associate mentioned. No specific action was taken on the third case, but cases (2) and (3) resulted in the Credentials Committee requesting interpretation of the present By-Laws of the College in regard to Associates who for sundry reasons, other than illness, but usually due to inability to attain certification, fail to qualify for advancement to Fellowship in the

maximal term, but then wish later to return to Associateship and in a limited period apply for advancement to Fellowship. Dr. Piersol pointed out the By-Laws provide that once an Associate is dropped for failure to qualify for Fellowship in the time provided, he may not thereafter apply for direct Fellowship. In the opinion of some members of the Credentials Committee, there may have been an attempt to circumvent the By-Laws by some Associates who, rather than being dropped, resign their Associateships, in order that they may later reapply for reinstatement as Associates for a temporary period, long enough to allow them to present their credentials for Fellowship, this being done after they have had an opportunity to complete certification and submit other adequate credentials. The Committee had received the applications of three former Associates who had been dropped, or who had resigned, for reinstatement for a temporary period, long enough to present the credentials for Fellowship. Since they were dropped they have completed certification and other qualifications. The question in point, raised by the Credentials Committee, was, can such an Associate be reinstated to serve the minimal Associate term of three additional years, or may he after reinstatement, immediately present his credentials for advancement to Fellowship, credit to be given for his first full term as an Associate?

There was long and extended discussion, finally resulting in the following resolution, moved by Dr. Maurice C. Pincoffs, seconded by Dr. Marion A. Blankenhorn, and carried:

RESOLVED, the recommendation of the Board of Regents to the Committee on Credentials shall be that Associates who have failed to qualify for Fellowship in the five-year period allotted by the By-Laws be dropped from the roll, or at their option may resign; if such individuals are again proposed in due form for Associateship, the Credentials Committee shall be under no commitment to accept them, except upon completely acceptable qualifications; and, furthermore, if they be re-elected to Associateship they shall not be eligible for advancement to Fellowship for a term of three years. This action shall not be retroactive, nor shall it affect those cases in which an extension has been granted for valid reasons.

The following additional resolution was adopted:

RESOLVED, that the Committee on Credentials shall notify each member of the Board of Governors of the preceding resolution and conditions related thereto.

On recommendation of the Committee on Credentials, the Board adopted a resolution extending for two additional years the terms of three Associates, because of illness or adequate and acceptable extenuating circumstances.

DR. PIERSOL (continuing his report): "The Committee on Credentials has reviewed the qualifications of 359 candidates for Associateship, recommending the following action:

Recommended for election to Associateship	273
Recommended for election to Direct Fellowship, because of Age and Outstanding Qualifications	2
Deferred	61
Rejected	23
	359

"Additionally, there were three candidates proposed for Direct Fellowship whose credentials were considered appropriate only for Associateship, and their election to Associateship recommended, making the total number of recommended Associates 276."

(By resolution of the Board of Regents, the group was formally elected, and their names have been published in a preceding issue of this journal.)

DR. PIERSOL (continuing his report): "The Committee also reviewed 144 candidates for Fellowship, and recommends the following action:

Recommended for advancement to Fellowship	90	
Recommended for election to Direct Fellowship	19*	109
Recommended for election first to Associateship		3
Deferred		26
Rejected		8
		144, plus 2*

* This refers to 2 Associate candidates who, because of age and outstanding qualifications, were accepted for Direct Fellowship."

(The Regents, by resolution, elected the group of 109 candidates to Fellowship, and their names have been published in a preceding issue of this journal.)

Dr. Piersol then presented the following report for matter of record on the group of Associates who were elected December 16, 1944, and whose Associate terms normally would expire at this meeting:

Already advanced to Fellowship	106
Deceased	2
Resigned	4
Terms extended because of military service, or other acceptable extenuating circumstances	55
Dropped for failure to qualify	16
Total elected, 12–16–44	183

Dr. Piersol further reported on miscellaneous Associates elected prior to December 16, 1944, five years ago, whose terms were extended due to military service until the autumn of 1949, and presented the names of 16 who, under the By-Laws, were at this time dropped from the Roster.

By resolution, the report of the Committee on Credentials was accepted in its entirety.

President Fitz requested the report of the Committee on Masterships, and Dr. Charles F. Moffatt, Chairman, gave the details of the proceedings of the meeting of that Committee and presented the nomination of Dr. Roger I. Lee, F.A.C.P., Boston, Mass., as the only candidate. Dr. Lee was selected because of his long period of activity in the College; he was a Regent from 1937 to 1941; President-Elect, 1941; President, 1942, and again served as Regent from 1943 to 1947. He is a member of the Board of Corporators of Harvard University and is associated with many outside medical interests in Boston and elsewhere.

By resolution, Dr. Lee was unanimously elected a Master of the College for induction at the Boston Session in April, 1950.

President Fitz then called for the report of the Committee on the Alfred Stengel Memorial Award, which was made by Dr. Maurice C. Pincoffs, Chairman, who, in accordance with the By-Laws, presented the nomination of three candidates who were voted upon by secret ballot and the recipient selected, to be announced at the annual Convocation of the College at Boston, April 19, 1950, when the Award will be made.

PRESIDENT FITZ: "Next is the report of the Committee on Educational Policy, by Dr. William S. Middleton, Chairman."

DR. MIDDLETON: "The Committee on Educational Policy defers to Dr. Thomas M. McMillan, Chairman of the Advisory Committee on Postgraduate Courses, for the complete report."

DR. THOMAS M. MCMILLAN: "These two Committees held a joint meeting. Mr. Joseph P. Hackel, of the Medical Film Guild, New York, N. Y., met with the joint committees and outlined certain exploratory suggestions whereby the College could benefit from the use of medical films. Specific proposals were quite nebulous and the

joint committees felt that, at the present time, the suggestions made are not practical, and that the College should not further consider this now.

"The committees considered a suggestion made by Dr. Nils P. Larsen, F.A.C.P., A.C.P. Governor for Hawaii, to the effect that the College aid postgraduate education in Honolulu, Australia and New Zealand. The committees felt that we were not in a position, at this time, to seriously consider postgraduate teaching in Australia and New Zealand, but they did feel that we should seriously explore the possibility of helping in postgraduate education in Hawaii. The combined committees felt that perhaps the most direct step would be to aid the Medical Society of the Hawaiian Islands in arranging a postgraduate course. To this end the committees felt that the College could be of real aid in helping to secure suitable teachers from its membership in the United States. The joint committees also felt that since the expense of such a venture is great, that the College might consider the possibility of helping in some way to defray the expenses of such a course.

"The results of the postgraduate courses given in 1949 were presented and discussed. The joint committees felt that the courses given in the spring of 1949 should be regarded as entirely successful, some 600 physicians having attended the nine courses given. The courses given during the autumn of 1949 (some of them have not yet been held) are also to be regarded as successful.

"Possible courses to be given in the spring of 1950 were discussed. The joint committees wish to recommend nine courses; of which it seems probable that one or more may not materialize. These courses are:

1. INTERNAL MEDICINE. University of California Medical School. Stacy R. Mettier, M.D., F.A.C.P., Director.
*2. PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. Duke University School of Medicine, Durham, N. C. Eugene A. Stead, Jr., M.D., F.A.C.P., Director.
*3. MECHANICS OF DISEASE. Peter Bent Brigham Hospital, Boston, Mass. George W. Thorn, M.D., F.A.C.P., Director.
4. CLINICAL ALLERGY. Roosevelt Hospital, New York, N. Y. Robert A. Cooke, M.D., F.A.C.P., Director.
5. CARDIOVASCULAR DISEASE. Michael Reese Hospital, Chicago, Ill. Louis N. Katz, M.D., F.A.C.P., Director.
6. ELECTROCARDIOGRAPHY. Massachusetts General Hospital, Boston, Mass. Conger Williams, M.D., F.A.C.P., Director.
7. ENDOCRINOLOGY. University of Illinois, et al., Chicago, Ill. Willard O. Thompson, M.D., F.A.C.P., Director.
8. DISEASES OF THE BLOOD VESSELS. Cornell University, New York Hospital, New York, N. Y. Irving S. Wright, M.D., F.A.C.P., Director.
*9. PSYCHOSOMATIC MEDICINE. Neurological Institute, New York, N. Y. Harold G. Wolff, M.D., F.A.C.P., Director.
10. CLINICAL ASPECTS OF MALNUTRITION. Hospital Enfermedades de la Nutricion, Mexico, D. F. Salvador Zubiran, M.D., F.A.C.P., Director.

(*These courses will be deferred, and substitute courses selected.)

"The joint committees are ready to recommend definitely, at this time, five courses to be given in the autumn of 1950. These are:

1. HEMATOLOGY. Boston, Mass. Dr. William B. Castle, M.D., F.A.C.P., or as alternate, William Dameshek, M.D., F.A.C.P., as Director.
2. INTERNAL MEDICINE. University of Pittsburgh School of Medicine, Pittsburgh, Pa. R. R. Snowden, M.D., F.A.C.P., Director.
3. GASTRO-ENTEROLOGY. University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa. Henry L. Bockus, M.D., F.A.C.P., Director.

4. INTERNAL MEDICINE. University of Utah School of Medicine, Salt Lake City, Utah. M. M. Wintrobe, M.D., F.A.C.P., Director.
5. INTERNAL MEDICINE (or some other course). Johns Hopkins University and University of Maryland Schools of Medicine, Baltimore, Md.

"Certain possible courses to be given during 1951 were discussed. The committees wish to recommend that the course in INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY be given by Dr. Marion A. Blankenhorn, F.A.C.P., in Cincinnati, Ohio.

"The committees also wish to recommend a course on the PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, to be given by Dr. Ray F. Farquharson, F.A.C.P., of the University of Toronto Faculty of Medicine, in Toronto.

"The committees also wish to recommend that some time in 1951 a course in INTERNAL MEDICINE be given by Dr. Howard P. Lewis, F.A.C.P., of the University of Oregon Medical School, Portland, Ore.

"Other possible courses for 1951 were discussed:

(a) On the Physiological Basis for Internal Medicine, by Dr. George E. Burch, Jr., F.A.C.P., of New Orleans, La.
(b) A course covering, in a broad way, the newer technics in the study of disease. The thought was that this course should, among other things, deal with the use of radio-isotopes in the clinical study and treatment of disease. No definite recommendation is made with regard to this course, except that the matter be explored further with Dr. McCann of the University of Rochester School of Medicine.
(c) It was also felt that a course in Internal Medicine, to be given at the University of Oklahoma, was well worth consideration for some future date."

PRESIDENT FITZ: "The report consists of three distinct parts: (1) it deals with films; (2) it deals with the Hawaiian matter, proposing that we study the situation further with regard to means by which the promotion of postgraduate teaching in Hawaii and Australia may be accelerated, but the Committee at present is not asking for funds, but merely wants to make a study; and (3) the approval of the Postgraduate Courses proposed in the report."

There followed a general discussion on the above three divisions. All were in favor of the Committees' report regarding the medical films. Discussing the Hawaiian situation, Dr. Middleton stated that he and several other Fellows of the College had been to Hawaii to participate in Postgraduate Courses of the Medical Society, that he had gotten the impression that our Fellows in Hawaii rather felt that they are stepchildren of the College, and that they might readily be entitled to a program of postgraduate education conducted on the order somewhat of a "Cook's Tour," and that Australia and New Zealand might be included. He thought the joint committees should investigate further the possibility of supporting our Fellows in the Hawaiian Islands in their efforts to get teams or individuals to come there to participate in postgraduate medical education. He said further that the College has a very strong representation in Hawaii, but numerically they cannot underwrite a postgraduate program themselves, but should like to have the support, moral and monetary, in carrying on a postgraduate program in which the College might readily coöperate with the Territorial Medical Society of Hawaii.

Dr. Cyrus C. Sturgis referred to some consideration being given this matter by the Committee on Fellowships and Awards, because the question had come up about the possibility of the Kellogg Foundation supporting such travel teams to Australia and New Zealand, but the Foundation, through its President, had as yet only expressed moderate interest, and the College had assured the Foundation of its readiness to cooperate at any time the Foundation was prepared to offer financial assistance.

(On motion by Dr. William D. Stroud, seconded by Dr. Maurice C. Pincoffs, and regularly carried, a RESOLUTION was adopted, leaving the matter in the hands of the Committee on Educational Policy for further study and later report.)

A RESOLUTION was unanimously adopted, approving all the courses recommended by the Committee and approving the report as a whole.

PRESIDENT FITZ: "We would like to have a report from the American Board of Internal Medicine, Dr. Truman G. Schnabel, Chairman."

DR. TRUMAN G. SCHNABEL: "Mr. President, the Board of Internal Medicine has functioned in the past year much as it has for some years in the past, being chiefly concerned with the matter of arranging for and giving examinations, both of a written and oral type. As a matter of information, we held our annual written examination on October 7 of this year in fifty-three different centers, including the European occupied zones, Tokyo, Saipan, Puerto Rico, Honolulu and the Netherland West Indies. 1,182 candidates took the examination. The coöperation of all proctors was superior. The score sheets have been forwarded to the Librarian, and it is hoped the results will be available by December 20. The task of determining the passing score and correcting score sheets is a major problem. Many are checked individually after machine correction. This requires much time, so that the completion of the entire job in two months is a minimum interval.

"For 1950 the Board has planned three oral examinations, one in Chicago on February 8–10; one in Boston, preceding the Annual Session of the College, April 13–15; and one in San Francisco, preceding the A.M.A. meeting, June 21–23. The matter of assistant guest examiners has always been a perplexing problem. A proposal to establish an official group of examiners is being explored.

"Elections during 1949 included the speaker's election to the Chairmanship, to succeed Dr. Hugh J. Morgan; the reëlection of Dr. Marion A. Blankenhorn as Vice Chairman, and Dr. Virgil P. Sydenstricker was made Secretary-Treasurer. New members of the Board include Dr. Henry M. Thomas, Jr., to succeed Dr. Hugh J. Morgan, and Dr. Albert M. Snell, to succeed Dr. Cecil J. Watson, resigned. Dr. T. Grier Miller was elected to the sub-specialty board on Gastro-enterology, to succeed Dr. Henry L. Bockus.

"Certain amendments in the By-Laws have been authorized:

(1) Effective July 1, 1949, the Board waived restrictions on the number of written examinations authorized, provided the candidate has satisfied the requirements set forth, but the Board at its discretion may deny reëxamination in any individual case, and the interval between the first and second written examinations shall be one year; the interval between subsequent examinations shall be two years, or longer. A fee of $10.00 is required for each additional written examination;

(2) Effective July 1, 1949, the Board waived restrictions on the number of oral examinations authorized, provided the candidate has satisfied specific requirements, but the Board at its discretion may deny reëxamination in any individual case. The interval between the first and second oral examinations shall be one year; between the second and third, not less than two years; and between subsequent oral examinations, not less than three years. A longer period may be required by the Board. A fee of $20.00 is required for each additional oral examination;

(3) Candidates have the privilege of electing a longer interval between repeated examinations, oral or written;

(4) When applying for reëxamination, a candidate who has been unsuccessful in three written or three oral examinations will be required to present evidence that he has completed additional graduate training of at least three months in an approved medical school on a full-time basis, or its equivalent in

approved resident or fellowship training. In individual cases the Board may require a longer course. Short courses of less than three months may not be applied in satisfaction of this requirement;

(5) The provisions of this section shall be effective retroactively.

"Any candidate who cancels his assignment for a written or an oral examination after the official cards of admission have been mailed will be required to pay a special fee of $10.00 before taking a subsequent examination, unless his cancellation was due to a cause deemed adequate by the Board to exempt him from such special fee.

"There were some changes to the Memorandum to Applicants. For admission to examination, all candidates must be active members in good standing in their county and state medical societies, in the state of legal residence. Under unusual or exceptional circumstances, the Board reserves the privilege of modifying this requirement. This ruling does not apply to commissioned officers of the U. S. Regular Army, Navy or Public Health Service, who are otherwise members of the A.M.A. Also the Board has a new regulation, granting training credit to commissioned officers in the U. S. Army, Navy or Public Health Service who served subsequent to December 7, 1941, and terminated their service on or before January 1, 1947. It provides that commissioned officers serving less than one year, prior to January 1, 1947, apply that interval as graduate training service. Credit training or practice beyond one year requires individual evaluation by the Credentials Committee."

Dr. Schnabel presented other details, including efforts toward activation of the Advisory Board for Medical Specialties, in coördinating work of various boards, the participation of the American Board of Internal Medicine on the Conference Committee for Graduate Training in Medicine, working with representatives of the American College of Physicians and the Council on Medical Education and Hospitals of the American Medical Association, and other matters. A resolution was adopted accepting the report with thanks.

PRESIDENT FITZ: "Dr. Alex. M. Burgess, Chairman, will now present the report of the Committee on Constitution and By-Laws."

DR. ALEX. M. BURGESS: "A separate Medical Service has been authorized for the U. S. Air Force. In a letter dated September 8, 1949, General Armstrong, the Deputy Surgeon General, brought the attention of the College to the fact that Officers of the Air Force should be entitled to the same setup in our Constitution and By-Laws as the Medical Officers of the Army, Navy and Public Health Service. The Committee, therefore, proposes the following additions to the By-Laws, providing that the U. S. Air Force, now a separate unit, shall have its Surgeon General on the Board of Governors, thus authorizing him to be the final endorser on all candidates for membership in the College from that Service:

By-Laws, Article IV, Board of Governors, section (1), line 7 to read, "Board of Regents; one each from the United States Army, Navy, *Air Force*, Public. . . ."

By-Laws, Article V, Election of Fellows, section (*2*), line 6 to be revised to read, he resides, or by the Surgeon General of the Army, Navy, *Air Force* or Public Health. . . ."

By-Laws, Article VII, Election of Associates, section (*2*), line 7 to read, "Navy, *Air Force* or Public Health Service or the Medical Director of the Veterans. . . ."

"The only amendment, therefore, is the insertion of the words "Air Force" at the three points indicated."

(On motion by Dr. A. B. Brower, seconded by Dr. Walter L. Palmer, and unanimously carried, these amendments were approved, and the Secretary was instructed to present them for final ratification at the next Annual Business Meeting of the College in Boston.)

PRESIDENT FITZ: "Next is the report of the Committee on Public Relations, Dr. LeRoy H. Sloan, Chairman."

DR. LEROY H. SLOAN: "The Committee met with all members present, with the exception of Dr. George F. Strong. Several items were presented by way of communication:

(1) Dr. John G. Archer, Governor for Mississippi, requested advice on conducting Joint Regional Meetings with the American College of Surgeons.
The Committee feels that in general they would discourage this suggestion, although rarely local conditions might justify such action.

(2) A proposal to the College for distribution of medical and scientific books to needy universities and professional centers abroad through 'CARE.'
The Committee is cognizant that European Countries do need new medical books and current medical publications. The Committee recommends that the College support in principle the general plan proposed, and that the College send, free of charge, a certain number of subscriptions to the ANNALS OF INTERNAL MEDICINE to special centers, and that individual members subscribe to the general idea covered in this proposal.

(3) The Medical Library Association solicited memberships and funds through the College.
The Committee feels this is not a College program, but is purely an individual situation. The Committee, therefore, recommends no action.

(4) A communication from Dr. Carlson, and others, concerning the National Society for Medical Research, in connection with animal experimentation.
It is now too late for action. Automatically, the problem has been disposed of for the time being, but that Society wishes to bring to the attention of the members of the College the necessity for their active coöperation with this group in the future.

(5) A communication from Dr. Marshall G. Nims, F.A.C.P., regarding staff meetings and the hospital accrediting plan of the American College of Surgeons.
A local group objects to the requirements of holding frequent staff meetings and points out that members of the staff of one hospital often are members of other hospital staffs; that there is duplication and the waste of much time. The Committee feels this is a local situation and a problem relating primarily to the American College of Surgeons and the Denver Society of Internal Medicine. It should be settled between the local group and the College of Surgeons.

(6) The Committee's attention was called to the fact that at least two Fellows of the American College of Physicians hold Fellowships also in the American College of Surgeons. One of our members is an Ophthalmologist, in good standing, who belongs to both Colleges and the Academy of Ophthalmology. The By-Laws of the College do not specifically deny this privilege, but it has been the policy of the Board of Regents to discourage the dual Fellowships in the A.C.P. and the A.C.S.
The Committee calls it to your attention without recommendation.

"The Committee recommends the acceptance of the following resignations:

Dr. Elsworth Fredrick Baker (Associate), Shrewsbury, N. J.
Dr. L. Clagett Beck (Associate), Honolulu, T. H.
Dr. Russell A. Garman (Associate), Jeannette, Pa.
Col. Milford T. Kubin (Associate), M.C., U. S. Army
Dr. Oliver T. Turner (Associate), Pittsburgh, Pa.

"The Committee recommends that, due to total incapacitation, by virtue of a cerebral hemorrhage, the dues of Dr. ....., shall be waived beginning January 1, 1950."

A resolution was adopted approving and accepting the recommendations of the Committee on Public Relations.

PRESIDENT FITZ: "Next is the report of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis, Chairman."

DR. STURGIS: "The Committee on Fellowships and Awards met at the College Headquarters on November 11, 1949, with the following in attendance: Dr. Cyrus C. Sturgis, Chairman, Dr. David P. Barr, Dr. Ernest H. Falconer, Dr. T. Grier Miller, Dr. Walter L. Palmer, President Reginald Fitz and Dr. Benjamin G. Horning, Director, Medical Division, Kellogg Foundation.

"The report of the Committee includes two meetings since the last meeting in New York City—the first meeting at Ann Arbor, Mich., on July 30, 1949, and the second meeting at the College Headquarters on November 11, 1949—with a full attendance of the Committee at both meetings:

"Latin-American Fellowship Program—The possibility of recommending Fellows from Australia and New Zealand and, perhaps, England was discussed by the Committee, and with Dr. Horning and Dr. Emory Morris of the Kellogg Foundation. It was concluded that in the future Fellows may be recommended from these areas, and also that 'travel teams' of teachers may be sent to Australia and New Zealand. It was the opinion of the Committee that we would gladly coöperate with the Kellogg Foundation at any time they cared to render financial assistance for these purposes.

"The Committee discussed the possibility of extending the Latin-American Fellowships to include applicants from Puerto Rico. These had previously been excluded because they are American citizens. It was voted to include applicants from this country. Latin-American Fellowships, therefore, at present are available in Mexico, Central America, South America, Cuba and Puerto Rico.

"The advisability of giving some type of Fellowship Certificate to the Latin-American Fellows was discussed. It was recommended that Dr. Walter L. Palmer and the Executive Secretary act as a Committee to bring in recommendations as to wording and form at the next meeting of the Committee.

"In connection with the meeting of the Committee in Ann Arbor, there were certain definite principles established in connection with the interpretation of the Latin-American Fellowship Plan, as follows:

(1) that the candidate shall have learned English prior to starting his Fellowship in the United States;
(2) that the Kellogg Foundation will make some financial allowance to compensate an institution for expenses incident to the training of these Fellows, and the Educational Center may bill the Foundation directly for such expenses;
(3) that the Latin-American Fellowships shall not be restricted to Internal Medicine, but may include the allied specialties represented within the membership of the American College of Physicians, such as Neurology, Psychiatry, Pediatrics, Pathology, Dermatology and Radiology;
(4) the Committee concluded that all Fellows coming to this country for further training should have an Orientation Course in American medical methods for a period from three to six months, and for that purpose the course already established at Cornell University will be utilized.

"The original Plan for the Latin-American Fellowships adopted by the Board of Regents at its last meeting was modified in minor detail and those modifications

have been approved by the Committee and will be recorded with the approval of the Board of Regents in these Minutes.

"At the meeting in Ann Arbor on July 30, 1949, three men were approved for Fellowships, namely:

1. Henrique BENAIM Pinto, Caracas, Venezuela
2. Rodolfo DE CASTRO Curti, Mexico City, D. F.
3. Horacio JINICH Brook, Mexico City, D. F.

"These men reported at Bellevue Hospital for the Orientation Course given by Cornell University under the auspices of Drs. J. J. Smith and E. Hugh Luckey. Dr. Benaim reported on October 1; Drs. de Castro and Jinich reported on September 1. These men reported for an interview with the Committee, and, following the discussion concerning their wishes with regard to future training, it was decided that Dr. Jinich might be assigned to Cornell University Medical College under Dr. David P. Barr as preceptor, and that Dr. de Castro could be assigned to the University of Michigan Medical School, under Dr. Cyrus C. Sturgis as preceptor. After some discussion, it was decided to ask the Chairman of the Committee to correspond with Dr. Herrman Blumgart, of Beth Israel Hospital, Boston, Mass., to inquire if he would act as preceptor for Dr. Benaim.

"Also approved at the Ann Arbor meeting on July 30, 1949, for Fellowships were the following, to start September 1, 1950:

4. Fructuoso BIEL Cascante, Concepcion, Chile
5. Roberto Figueira SANTOS, Salvador, Brazil.

"The following new applicants for Latin-American Fellowships were considered at this meeting, November 11, 1949:

1. Jacques TREMBLAY, Montreal, Que., Canada
   The Kellogg Foundation has already on its own authority placed this candidate in the Orientation Course at Cornell, but action by the Committee on Fellowships and Awards of the College will be deferred until his progress at Cornell has been established.
2. Egon LICHTENBERGER Salomon, Bogota, Cundinamarca, Colombia
   Fellowship approved; to be assigned for three months to the Orientation Course at Bellevue Hospital, and at that time an attempt will be made to place him with Dr. Moritz, Professor of Pathology at Western Reserve University School of Medicine.
3. Francisco VON LICHTENBERG Schneider, Mexico, D. F.
   Fellowship approved; Orientation Course not required; arrangements already concluded to work under Dr. Klemperer at Mount Sinai Hospital, New York, N. Y., in Pathology."

(On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Walter L. Palmer, and carried, the report on the Latin-American Fellowship Program to this point was approved.)

DR. STURGIS (continuing his report): *"Research Fellowships*—The Committee recorded that the six 1948–49 Research Fellows, who started July 1, 1948, concluded their work on June 30, 1949, and received from each candidate a detailed report of the work accomplished and manuscripts or publications emanating therefrom. The Committee was impressed with the satisfactory work accomplished by these Fellows. It was recommended by the Committee that the Executive Office in the future collect individual reports also from the preceptors under whom these Fellows work, for the permanent records of the College.

"A year ago the College awarded 8 Research Fellowships, 7 of whom have been at work since this past summer, and whose work is progressing well. One Fellow, Dr. James K. DeVore, resigned, due to uncertain problems of health, and the appropriation of $2,200.00 for him has been carried over for use toward the next group of Fellows, the 1950–51 Research Fellows.

"Of the 15 remaining applicants, 6 were selected for Research Fellowships, 1950–51, varying from $2,400.00 to $3,200.00 per annum, to wit:

1. *Edward Harvey Estes, Jr.;* 24; a graduate of Emory University School of Medicine, 1947; to work under Dr. James V. Warren, Department of Physiology, Emory University School of Medicine, on the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circuit.
2. *Dalton Jenkins;* 31; a graduate of University of Colorado School of Medicine, 1943; to work under Dr. George W. Thorn at the Peter Bent Brigham Hospital, Boston, Mass., on a study of the adrenal hormones on specific metabolic functions, with particular relationship to muscle metabolism.
3. *Edward Howell Lanphier; 27*; a graduate of University of Illinois College of Medicine, 1949; to work under Dr. Julius H. Comroe, Jr., Department of Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., on the investigation of new functional tests of the cardio-vascular-pulmonary system.
4. *William Andrew MacIlwaine; 27*; a graduate of University of Virginia Medical School, 1947; to work under Dr. Byrd S. Leavell, Associate Professor of Medicine, University of Virginia Department of Medicine, Charlottesville, Va., to study the effects of various procedures and substances on hemoglobin metabolism in sickle cell anemia.
5. *Cheves McCord Smythe; 25*; a graduate of Harvard Medical School, 1947; to work under Dr. Stanley E. Bradley, Department of Medicine, Presbyterian Hospital, New York, N. Y., on a problem concerned with renal and hepatic physiology as studied by blood flow technics.
6. *William Jape Taylor; 25*; a graduate of Harvard Medical School, 1947; to work under Dr. J. D. Myers, Department of Medicine, Duke University School of Medicine, Durham, N. C., to study the effects of insulin, epinephrine and adrenal cortical substances on the splanchnic glucose, phosphate and potassium intakes and outputs; also to study the effect of parenteral fat on hepatic blood flow and oxygen consumption.

"The following candidate, Dr. Edward Harvey Estes, Jr., was selected from the above group of six to be designated as the Alfred Stengel Research Fellow."

(On motion by Dr. Cyrus C. Sturgis, seconded by Dr. Maurice C. Pincoffs, and carried, the report on the Research Fellowships was approved.)

DR. STURGIS (continuing his report): "The Committee has nominated Dr. Edward Calvin Kendall, of the Mayo Clinic, Rochester, Minn., to receive the John Phillips Memorial Award for 1950. Dr. Kendall is well known for his biochemical studies in medicine, especially for his isolation of thyroxine and his study of steroid chemistry.

"Dr. Kendall is nominated particularly in recognition of his study of the chemistry of the thyroid gland, his investigation on the isolation of thyroxine and the chemistry of suprarenal cortex. We in no way nominate him on the basis of any implication that he was the discoverer of compound E, or that he should share particularly in that, but primarily on the basis of his long work in isolating thyroxine in 1914. He is 63 years of age, a Ph.D. in biological chemistry, and has been at the Mayo Clinic for thirty-five years."

(On motion by Dr. Walter B. Martin, seconded by Dr. Wallace M. Yater, and carried, the Board elected Dr. Edward Calvin Kendall as the John Phillips Memorial Medalist for 1950.)

DR. STURGIS (continuing his report): "The Committee has nominated Dr. Karl Friedrich Meyer, of San Francisco, Calif., to be the third recipient of the James D. Bruce Memorial Award, 1950. Over many years, Dr. Meyer has made many significant contributions in the field of public health.

(On motion by Dr. LeRoy H. Sloan, seconded by Dr. Alex. M. Burgess, and carried, Dr. Karl Friedrich Meyer was elected as the James D. Bruce Memorial Medalist for 1950.)

(On motion by Dr. Hugh J. Morgan, seconded by Dr. LeRoy H. Sloan, and carried, the report of the Committee on Fellowships and Awards was accepted as a whole.)

PRESIDENT FITZ: "Next is the report of the Committee on the Annals of Internal Medicine, Dr. Cyrus C. Sturgis, Chairman."

DR. STURGIS: "Present at the Committee meeting were Dr. Maurice C. Pincoffs, as Editor, and Drs. William S. McCann, Walter B. Martin and Cyrus C. Sturgis. The first recommendation the Committee desires to make is an increase in the advertising rates. Previously the Board has increased the subscription rates from $7.00 to $10.00, domestic, and from $8.00 to $11.00, foreign; the amount deducted from dues for the ANNALS, likewise, was increased from $6.00 to $9.00. On November 1, 1948, the printers increased their rate 23%, and the operating statements for the journal clearly reveal the marked increase in cost. The volume of scientific matter for the last year has increased 257 pages; news notes decreased slightly; and advertising decreased slightly. The latter is in accordance with experience by other publications, except that the decrease in advertising in the ANNALS has been less than in most journals.

"Our circulation is very flattering. In the past year it has increased more than 1,200 copies per month, and we are at present printing 13,500 copies. The financial report shows, in spite of additional subscriptions and fairly comparable advertising, a decrease in the net surplus of slightly over $4,000.00. The Executive Secretary has made a very careful analysis of the operating experience of the ANNALS and has placed a copy in your hands, which constitutes a part of our report. He has also made a careful comparable analysis of advertising rates in other journals. We recommend an increase in the avertising rates of 50% over those presently in effect. Our current rates remain as established in 1945, when the circulation was about 7,000 copies per month. Since that time it has increased 93%. The cost of printing this additional quantity obviously is very considerable. We were surprised to find out how low our advertising rates are in comparison with other medical journals in our field. For example, a full-page advertisement in the ANNALS OF INTERNAL MEDICINE is $70.00; a full-page advertisement in the American Journal of Medicine is $200.00; in the American Review of Tuberculosis, with a circulation of only about 6,000 copies, $90.00. The increase we recommend is very modest and should be put into effect on or about March 1, 1950, at the discretion of the Executive Secretary."

(On motion by Dr. Cyrus C. Sturgis, seconded by Dr. T. Grier Miller, and carried, this portion of the report was approved.)

DR. STURGIS (continuing his report): "The Committee discussed with the Editor the request of United Nations for exchange of various types of journals and information, much irrelevant to medicine, with the ANNALS OF INTERNAL MEDICINE. We feel that we have nothing to trade and nothing to gain by entering into such an agreement, and recommend that we not participate in the United Nations exchange proposition.

"The Committee received a request from a Mr. Powers of the University Microfilms, Ann Arbor, Mich., requesting permission, after the lapse of one year, to microfilm a whole Volume of the ANNALS OF INTERNAL MEDICINE. Permission would have to be granted, because this is copyrighted matter. Mr. Powers suggests that the cost of microfilming copies of the journal would be comparatively small. Libraries could dispose of the copies of old journals, thus saving valuable space, and store the microfilms for future reference. The Committee sees no particular harm in this proposal if the microfilming is deferred for one year from the date of publication of the AN-

NALS. It would not then interfere with the sale of the journal. There should be a proposal in any agreement providing for terminating same."

(On motion by Dr. LeRoy H. Sloan, seconded by Dr. Maurice C. Pincoffs, and carried, the Executive Secretary was authorized to enter into an agreement that shall be in accordance with the opinions expressed in discussion by the Board.)

PRESIDENT FITZ: "Next is the report of the Conference Committee on Graduate Training in Medicine, Dr. LeRoy H. Sloan, Chairman."

DR. SLOAN: "Your Committee met with the members of this Committee at Atlantic City in June. This Committee is actively at work with the program of the evaluation of hospitals for residencies, working with representatives from the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. Dr. William S. Middleton is Chairman. The task immediately before the College is to develop a list of regional advisers who will act with the Committee in the evaluation, particularly of the professional teaching program of various hospitals for residencies in medicine. This list is being prepared and some replies have already been received in that connection."

DR. MIDDLETON: "The Conference Committee is a reactivated committee. It was in operation before the War and then discontinued until June of 1949. The task that confronted it at the time of reactivation was rather complicated by the thrusting upon it of a host of decisions as to the adequacy of residency training in a number of hospitals. The Committee as a whole felt it was not yet competent to pass upon these, and to implement its ends this plan of regional advisers was set up. Dr. Sloan is enlisting the support of the College in the naming of these men, because they must come from the College. After the group of regional advisers has been nominated and approved, the work will go forward quite regularly. Dr. Sloan has suggested a smaller subcommittee that can clear routine matters in the office of the Council on Medical Education and Hospitals. It will be explored further and considered at a meeting of the Conference Committee on February 7 at Chicago, at which time we can really initiate a program of coöperation with the Council that will insure to the Rating Board and to the Board of Internal Medicine advice that will be authoritative. Our slight delay in the outset will be made up by further expedition later on."

PRESIDENT FITZ: "We accept this as a progress report. Next will be the Treasurer's report by Dr. William D. Stroud."

DR. WILLIAM D. STROUD: "The report of the Treasurer is merely supplemental to that of the Committee on Finance. The cash balance on October 1, 1949, was as follows:

Endowment Fund	$ 61.96
General Fund	104,669.09
	$104,731.05

"It is estimated that there will be some $34,000.00 additional receipts and approximately $61,000.00 expenditures between October first and the end of the year. The Committee on Finance will make recommendations concerning the investment of surplus funds not required for operations, and it will also report the record of security transactions since the last meeting of this Board.

"The present security holdings of the College are as follows:

	Book Value	*Market Value*	*Appreciation*
Brower Fund	$ 5,000.00	$ 5,000.00	
Bruce Fund	10,000.00	10,000.00	
Endowment Fund	305,824.43	318,447.00	$12,622.57
General Fund	189,815.82	204,660.89	14,845.07
	$510,640.25	$538,107.89	$27,467.64

"The annual cash income from these securities amounts to approximately $23,000.00 per annum, and the average yield is 4.20%.

"The services of our Investment Counselor, Drexel & Co., appear to your Treasurer to be entirely satisfactory."

(On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Cyrus C. Sturgis, and carried, the report was accepted.)

President Fitz then called upon Dr. A. B. Brower, Chairman, to present the report of the Committee on Finance. Dr. Brower presented recommendations of the Investment Counselors for sale and purchase of certain securities, which were approved by the Board of Regents. He then presented the recommendation that the College reimburse Governors for one-half of their transportation costs, including pullman and lower berth fares, to the Annual Session at Boston, 1950, as an experiment. The College had not previously felt financially able to bear any part of the expenses of the Governors. This recommendation was by resolution approved by the Board of Regents.

Dr. Brower then presented detailed operating statements for the year 1949, as prepared by the Executive Secretary, and pointed out that the net estimated surplus for 1949 would be approximately $24,000.00, compared with $16,600.00 in 1948. The College is expected, he said, to operate about $16,000.00 within the original budget appropriations for 1949. Thereafter, the detailed budgets for 1950 were reviewed, showing an estimated income of approximately $241,000.00 and estimated expenditures of approximately $192,000.00. The budgets, by resolution, were approved, and the report of the Committee on Finance was approved as a whole.

President Fitz then reviewed in some detail the plans for the Thirty-first Annual Session in Boston, April 17–21, 1950. Some of the special features included clinics televised in color from one of the hospitals to Mechanics Hall, the headquarters for the meetings, this program being provided by Smith, Kline & French, so far as equipment, operation and costs are concerned. Dr. Fitz emphasized that Dr. Lewis Dexter, Chairman of the Committee on Clinics, will really give color television from the point of view of medical demonstration a very good trial. Dr. Fitz proposed to the Regents that Lord Moran, President of the Royal College of Physicians of England, be brought to Boston as the Convocational Lecturer. Lord Moran is a good public speaker, is a decorative figure and would represent the Royal College of Physicians very adequately, he said. This proposal was approved by the Board of Regents.

At the Banquet the Boston committees propose having President Conant of Harvard as the speaker. The program for the General Sessions and Morning Lectures is well developed, and will be published in the February, 1950, issue of the ANNALS OF INTERNAL MEDICINE and published simultaneously as a separate program to the members of the College. A special feature of the General Sessions Program, according to President Fitz, is the assignment of a block of the program to be given entirely by former Research Fellows of the College. Having both the General Chairman, Dr. Keefer, and the President in the same city, Dr. Fitz pointed out that it is much easier to coördinate all of the programs of clinics, panels, lectures and general sessions. By way of recreation, the Boston committees plan a concert by the Boston Symphony Orchestra on Monday evening, April 17, and many other unique and new arrangements, not only for the scientific program, but for the entertainment of the guests, including ladies, are planned.

By resolution the Secretary was authorized to prepare a testimonial certificate for the Director of the Boston Symphony Orchestra, and it was voted to confer an Honorary Fellowship upon Lord Moran, if he is obtained as the Convocational Lecturer.

President Fitz referred to 1938 when the plan was first introduced of having an annual dinner of the Regents, Officers and Governors, with the proposal of discussing some topic centered around matters of policy for the College in which both Regents

and Governors might equally engage. He proposed to reactivate that plan and at Boston choose as the subject for discussion the size of the College. He will select certain leaders who have long been connected with and interested in the subject to direct the discussion. He pointed out that if one were to plot a graph one could readily observe that in a few years from now the College would have such a large membership that to all intents and purposes it would be forced to meet in some such auditorium as that at Atlantic City, as there would be no other place large enough to accommodate the College.

It was then announced that the next meeting of the Committee on Credentials would be held at Philadelphia on March 19, 1950, and a succeeding meeting at Boston on April 15, 1950; that the next meeting of the Board of Regents would be held in conjunction with the Board of Governors at Boston on Sunday, April 16, 1950.

Adjournment.

Attest: E. R. LOVELAND,
Secretary.

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A. C. P. DIRECTORY

The 1949 Directory of the American College of Physicians, completely revised and republished as of October 1, 1949, has been completed and distributed by mail to those who had placed pre-publication orders.

It will not be republished until 1951, but a supplement will be issued during the autumn of 1950.

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4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

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